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⑥ nutritional factors
⑦ nutrients ⑧ prematernal care ⑨ postnatal care
⑩ prenatal care
⑪ child nutrition

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MATERNAL NUTRITION AND CHILD HEALTH
AN INTERPRETATIVE REVIEW

by
KIRSTEN UTHEIM TOVERUD, GENEVIEVE STEARNS AND
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Prepared for
The Committee on Maternal and Child Feeding of
the Food and Nutrition Board,
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and Alfred H. Washburn.

*Deceased

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This volume is the third report prepared by the Committee on Maternal and Child Feeding for the Food and Nutrition Board. The first report, "The Advisability of Breast Feeding," was published in the Journal of the American Medical Association for December 6, 1947. The second, "The Composition of Milks," was published as National Research Council Bulletin No. 119, January 1950. A report on adolescent nutrition is in preparation.

The board is greatly indebted to the Committee for these most helpful contributions.

Frank G. Boudreau, M.D.
Chairman, Food and Nutrition Board

FOREWORD

The Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council, felt that a comprehensive, world wide survey of our present knowledge of the nutrition of the mother in relation to the health and vigor of her infant at all stages of his development would serve important needs of obstetricians, pediatricians, and other workers concerned with problems of maternal health and child growth and development. To bring together the information published in the journals of many countries and to evaluate studies made under widely variant conditions required a discerning investigator thoroughly conversant with the problem. Kirsten Utheim Toverud, M.D., of Oslo, Norway, was chosen because in the course of a professional life spent largely in this field, with publications throughout a quarter of a century, she had been one of the first experimentalists to demonstrate clearly the far-reaching effects of maternal nutrition, not only on the structure of the fetus but also as the factor which, in large measure, influences the future growth and development of the child. For a quarter-century "The child is nutritionally 9 months old at birth" had been the working hypothesis of Dr. Toverud in the experimental and clinical research which resulted in many significant contributions to our knowledge of nutrition.

In addition to her experimental work with animals and the application of the findings to human mothers, Dr. Toverud was able to visualize and establish an experiment in public health which has become known the world over. Through her efforts the city of Oslo granted the establishment of a prophylactic prenatal and postnatal health station, or health clinic as it would be called in the United States. Morbidity and mortality statistics were acquired which proved Dr. Toverud's thesis that maternal and infant mortality can be greatly reduced if available knowledge is properly utilized.

Dr. Toverud came to this country for six months in 1948 as a guest of the Children's Fund of Michigan and during that time was able to lay the foundation for the present publication. Her vision, developed by years of practical experience in the field, her unstinting personal effort, and her conviction of its importance impelled her to approach the problem from every possible angle. With her prepared mind she uncovered relevant information which would have been missed by others. While collecting her material Dr. Toverud divided her time between the Research Laboratory of the Children's Fund of Michigan and the State University of Iowa, where the staffs provided every facility and service which would assist her efforts. The co-authors of this report collaborated with Dr. Toverud in selecting, reviewing, and interpreting the literature.

Dr. Toverud chose the material she wished to use in her review and wrote sections outlining her thinking before it was necessary for her to return to Norway. Unfortunately, her subsequent illness and untimely death made it necessary for others to assemble her material, add current references, and complete the manuscript. The bulk of the responsibility for converting Dr. Toverud's material into this manuscript was assumed by Ralph E. Sloan, editor for the Research Laboratory of the Children's

Fund of Michigan. The wording of the presentation is not that of Dr. Toverud, but every effort was made to preserve her vision, to record in English her experimental results, and to emphasize her unique contribution to the welfare of future generations of mothers and their children. To ensure achievement of these objectives as well as a greater measure of accuracy, the semi-final draft of the manuscript was submitted for criticism and approval of final content to Dr. Güttorm Toverud, Professor of Pedodontia, Dental School of Norway, Oslo, Dr. Philip C. Jeans, Professor of Pediatrics, State University of Iowa, and Dr. J. P. Pratt, Chief of the Department of Obstetrics, Henry Ford Hospital, Detroit. To these individuals and to Dr. Genevieve Stearns, all of whom gave freely of their time and energy in the interest of this project, the Committee wishes to extend grateful acknowledgment.

—Icie Macy Hoobler, *Chairman*
Committee on Maternal and Child Feeding

PREFACE

At the National Health Assembly in May, 1948, it was recognized that "from Pearl Harbor to V-J Day, 281,000 Americans were killed in action. In the same period, 430,000 babies died in the first year of life. Many of these deaths were preventable." The mothers and infants who die disappear from sight, but factors involved in reproduction also leave an army of handicapped and mentally defective children and weakened and anxious mothers scattered throughout the world.

Are inferior progeny and damaged mothers the inevitable result in a large percentage of pregnancies? Is childbearing a risk in which success is subject to laws of chance? We think not. Knowing how perfectly Nature has planned the bodies of various species to assure their perpetuation it seems more likely that failures in reproduction are the result of external influences, conditions which do not fulfill the demands imposed by Nature's basic laws. Knowledge gained only since the beginning of the present century indicates that better understanding of the role of nutrition in reproduction would result in greatly decreased mortality and morbidity among both mothers and infants. If mothers were in a nutritionally adequate condition prior to conception and received an adequate diet during pregnancy and lactation, supported by sound medical guidance throughout, maternity would be less hazardous and children would be more apt to receive their rightful nutritional heritage.

Mature human beings equipped with the mental and physical health necessary for them to function at maximal capacity can only result from optimal conditions of external and internal environment throughout the period of their growth and development. For any individual the initiation of these maturation processes coincides with the union of sperm and ovum. When these processes have been fully explored and the laws of growth and development are completely understood, it will be possible to plan adequately for the well-being, happiness, and physical efficiency of mothers and for the greatest possible development of new generations.

Growth and development include the formation of tissue, whether as a part of a reparative process or as an expansion of body structure. We talk about intrauterine growth and the growth in size (weight, length) which occurs from birth to the eighteenth or twentieth year of life, but at present we are still at a loss for a word describing the growth process in the maternal body during the sexual cycle. In women, growth continues at a varying rate until the end of the sexual cycle at 40 to 50 years of age. In men we do not know when growth stops and when full maturity is reached. For both sexes it is a question if full maturity may be considered to have been reached when the skeleton is fully developed and the third molar has erupted, which may be any age from 18 to 30 years (or never).

The so-called "physiological growth" of women which continues after the characteristic body weight and length of the individuals have been attained ceases only with termination of the reproductive period of life. During menstruation, pregnancy, lactation, and postpartum reparative periods, metabolic processes present nutritional requirements which correspond closely to those of growth in size. All of these physical states increase the body's need for the various nutritional factors, and the requirements for some food components may be increased more than those for others.

The prematernal period in which the body develops its potential for childbearing also must be considered a segment of the reproductive cycle and a factor of major importance in relation to maternal and infant nutrition. The stores of some nutritional factors in the mother organism prior to pregnancy have been shown to be of great importance to the future health of mother and child. If pregnancy occurs during the years of adolescence when the maternal organism itself is still developing, the maternal body must continue to fulfill the nutritional requirements for its own growth and development and meet those of the fetus concurrently.

For the past 25 years intensive studies have been made in various countries to determine the value to mothers and infants of thorough and systematic supervision of women during their reproductive periods. Data from scientific studies in this field, coupled with results from the practical application of the newer knowledge of nutrition which are now accumulating, confirm that the well-being of the unborn child is influenced greatly by the mother's nutritional state before and at the time of conception. From various parts of the world contributions from the nutritional point of view, from the bioenergetic, the anatomical, the statistical, the social, and the mental points of view have made fundamental contributions to our understanding of the complex processes combined with growth and development of an individual. In the United States especially, groups of workers have been engaged in cooperative, long-time, clinical and experimental research upon various aspects of the nutrition of mothers and infants.

For those of us who for years have been deeply interested in nutritional aspects of the entire growth period and have had some awareness of the great possibilities in improved diets and adequate medical supervision as means to promote the health and happiness of mothers and children, it is a great satisfaction to follow the data now accumulating. In this publication we have assembled significant material indicating the progress which has been made in reducing maternal and infant mortality and morbidity and profitable directions for further experimentation, with the hope that this compilation will stimulate and facilitate application of knowledge now available.

—Kirsten Utheim Toverud

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INTRODUCTION

The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition.

July 22, 1946, sixty-one nations signed the constitution of the World Health Organization, dedicated to the concept that peoples of the world cannot exist half-sick and half-well, any more than they can exist half-slave and half-free. Each of the signatories realized that the solution of economic, social, and food problems is contingent upon the concerted efforts of all nations and all races.

Recognition of specific values in food and important environmental factors in its utilization is not new. The use of liver was recommended in the Ebers Papyrus in 1500 B.C. In the fifth century B.C., the remarks of Hippocrates evidenced the first organized thinking denoting recognition of what we term nutrition. Until the First World War, however, the full import of nutrition was realized by only a few physicians and scientists. The knowledge gained from investigations stimulated by the exigencies of the war years provided the impetus for broader and more intensive research into the physiological and chemical aspects of health. As one nutritional factor after another was discovered and their roles in the health of human beings were clarified, progress was made toward a better understanding of the importance of food and environment to the vitality of human beings.

Early in the history of nutrition as a science, study of foods by chemical methods clarified our recognition of various nutritional factors present and aided our evaluation of the few substances which then were considered important. Voit (1881) in Germany and Atwater (1895) in America tabulated the chemical composition of extensive lists of human foods. Then, biological analyses of food demonstrated the presence and importance of hitherto unknown components of foods. This era opened with the classic experiments of Lunin (1881) showing that adult mice invariably died within a month if they received a ration composed of what he believed to be the essential ingredients of milk—casein, butter fat, milk sugar, and the ash of milk. Neither this fundamental experiment nor the epoch-making observations of Eijkman (1897) that polished rice induced polyneuritis in birds and rice polishings relieved the condition received the attention they deserved.

The linear growth of a human being is initiated at conception but we cannot yet determine when full maturity is reached in an individual. Though growth in length usually ceases at an age of 18 to 21 years, full maturity of the skeleton may not be accomplished for several additional years. The periods of prenatal growth and infancy are the foundations of adult structure, both physical and mental, and it is practical to consider development as a chain whose links reach from conception to menopause, when reproductive functions cease.

A newborn baby is not a well-integrated organism starting life with unbounded possibilities. It is merely an organism which has gone through a difficult and sometimes violent and riskful ordeal, delivery, to start its independent life. Nutritionally the newborn infant is the result of a long series of metabolic processes within the

mother, which, in turn, were the result of metabolic processes in the maternal (and paternal) body previous to pregnancy and *ad infinitum*.

In early years some insight into the metabolism of mother and fetus was gained by chemical analyses of the fetus at various stages of development, and by metabolic studies of the mother organism. The majority of the subjects of early metabolic studies were women from the higher economic groups, and, of course, only the nutritional factors known at that time were investigated. In recent years anatomic, physiologic, dietary, and clinical studies also have been used to evaluate the processes occurring during pregnancy.

The earliest methods used to study maternal requirements during pregnancy were: (1) analysis of fetuses that came to autopsy because of some accident, abnormal condition of the mother, developmental defect, or physiologic dysfunction of the fetus itself; (2) metabolic balance studies which included the analyses of food eaten over a given period of time, and of the urine and feces excreted. The difference between the food eaten and the total excretion estimates the amount of nutriments assimilated by the mother for use in nourishing her own body tissues and those of the developing fetus. The earliest available record of fetal analyses was published by Von Bezold in 1858. In 1894, Zacharjewski undertook the first metabolic balance study of nitrogen during pregnancy. It was not until 1910, however, that Hoffström analyzed the food, urine, and feces of a woman for nitrogen, calcium, phosphorus, and magnesium during consecutive metabolic balance periods from the seventeenth week of pregnancy to term.

In 1911 Osborne and Mendel showed in rat experiments that a single protein was not able to maintain health over longer periods of time and that the criteria of adequate nutrition are quite different in the case of growing animals from those applying to adults of the same species. They also showed that a deficiency may exist long before it is evidenced clinically. Deficiencies may not occur until the second or third generation litters have depleted the various nutritional stores.

During and following the First World War it became clear that in human beings also the growing organism is influenced first by scarcities in food supply. The nutritional disorders found following that war were primarily in the most rapidly growing organism, the infant. The rachitic processes in the infants of Germany and Austria around 1920 opened an era of intensive investigation into the causes of this common and marked disturbance. In the years following the war great strides were made in the prevention of this disease as McCollum, in America, and Mellanby, in England, demonstrated the presence of a fat-soluble vitamin in cod liver oil and the need of this factor by the growing organism for normal calcification of the skeleton.

The events coincident to the First World War did not, however, demonstrate the significance of the fetal period in the future life of the individual, and the less obvious implications of some of the conditions found at that time were overlooked. The alarming numbers of marked rachitic disturbances discovered during and after the war were not considered in connection with possible deficiencies during pregnancy which might have affected the development of the fetus after depletion of any amounts in storage in the maternal body. The infant's postnatal life was the center of interest at that time and, without the knowledge which has become available in

the past 25 years, workers were misled by superficial evidence. During the hunger period in Germany the fact that often the birth weights of the infants were not lower than before the war was accepted as evidence that infants were not damaged even if their mothers had received diets limited in both quantity and quality. Until recently the belief was general that the diet and general health status of the human mother during pregnancy were of minor importance to the development of the fetus and, frequently, obvious pathological symptoms were necessary before pregnant women were placed under observation to determine dietary adequacy and hygienic environment.

Evidence from the results of the First World War was to many a corroboration o the belief that the fetus does not suffer from nutritional deficiencies of the mothe but is a parasite capable of drawing on the maternal organism for whatever is needed for growth during fetal life. The oestrus cycle in rats was thoroughly studied by Long and Evans (488) and the animal studies of Byfield and Daniels (103), and Korenchevsky and Carr (443), in 1923, and Mellanby (553, 555), in 1926, showed that this is not true: the mother organism is depleted when the deficiencies are marked. Through the extensive work of Scammon and Calkins (737) we have been able to reconstruct the anatomical growth and development of the fetus, and intensive study of the nutritional need during this period demonstrates that conditions formerly considered strictly hereditary and unpreventable may be due to malnutrition at some particular stage of development and hence preventable.

Early animal experiments plainly demonstrated that fetal damage may result from prenatal dietary deficiency. As early as 1911 Hart and associates (340) described the effect of different rations upon growth and development of the offspring. When heifers were fed more corn they became healthy and sleek and gave birth to full-term vigorous young, able to stand and suckle within an hour after birth. All young developed normally. The young of wheat-fed mothers, however, had a rough coat, were small, were born prematurely, and often were stillborn or died within a few hours. The cows fed oats were in between the two other groups. Later, they found that the wheat ration could be made satisfactory by the addition of bone meal and cod liver oil.

The science of nutrition which has developed in the past twenty-five years utilizes the combined knowledge of all fundamental and applied sciences. Even sciences such as theology, philosophy, and psychology are intimately involved in nutrition, owing to their involvement in psychosomatic relationships in the body. Consideration of problems of growth and development have assumed increasing importance, and many groups of specialists have pooled their resources and efforts to enable comprehensive studies of actions and reactions within growing human bodies and of the bodies in their entirety, at different ages and under various conditions. Nutrition has been approached from many directions—the bioenergetic, the anatomical, the statistical, the social, and the mental points of view, in addition to those of the physician, biologist, and chemist.

Reviewing the literature of different countries introduces many problems, for studies from various parts of the world cannot be directly comparable for many reasons. Both the physical and the dietary environments may differ widely from

study to study. The subject of one study may be on a far different plane of nutrition than a subject of a similar study in another part of the world. Adding to these variants differences in methods and in treating of data it becomes obvious that direct comparison of the results of the different studies is not always possible. The methods used in the earlier studies were the best available at that time but were less specific than some of the recent, more accurate ones. Nevertheless the ground work for our present knowledge was laid by the use of these same methods. With full cognizance of the limitations of the methods used and the astuteness of the researcher in observation and interpretation, very valuable contributions have been made in showing the scope of the problems involved and in approaching the solution to them. An attempt has been made to present on the following pages the scope of many of the problems involved, both experimental and observational, and to point out areas for profitable extension of research and application of results in our efforts to promote the health and vitality of human beings by enhancing the endowment with which they start their lives.

I

MATERNAL AND INFANT MORTALITY

Maternal mortality records throughout history have shown that for women of all races and in all lands the period of reproduction is one of risk, since pregnancy, parturition, and lactation make extraordinary demands upon their bodies and are accompanied by additional health hazards. General agreement is that infant deaths during the first months of life are traceable to factors that are damaging to the mother as well as to the infant, and that many infant deaths in the first and later months of life are preventable. Parks' (653) observation illustrates the inter-relationship: "Since the majority of obstetric complications have a more profound effect on the fetus than on the mother, infant mortality is a more delicate index of good obstetrics than is maternal mortality."

In reports on maternal and infant mortality, social and economic factors appear equally as important as the level of medical care, and a country's infant mortality therefore mirrors the hygienic standard of the population. In oriental and South American countries, with their prevalence of insufficient food, little medical care, and less education, mortality statistics are consistently higher than those from most of the Northern European countries. In some large areas, such as South Africa, India, and Brazil, figures are available only for principal cities or for the European population exclusive of natives, while the extent of mortality in the vast, primitive, rural areas is not known. In such areas advances in public health and improvements in the basic standard of living are primary to any reduction of the high death rates for mothers and children. Problems of maternal mortality, infant mortality, and stillbirths are essentially one because improvement of one rate must be accompanied by improvement of the other two.

Prior to the nineteenth century, vital statistics for the general population of European countries were available only for specific urban areas or for short periods of time. Vital statistics for the group of royal families of Europe, on the other hand, were assembled with far greater accuracy. Peller (664) surveyed the records of 2,848 female members of ruling families living between 1500 and 1899, of whom 2,099 were married, 749 were spinsters, and all but 61 were above 15 years of age. Mortality rates in the ruling families might be expected to be lower than those in the contemporary population owing to more favorable social, economic, medical, and hygienic circumstances. Control of mortality did appear to be many decades in advance among the upper class, but for some age groups mortality rates for the low nobility and peasants seemed to be better. Over the four centuries, the percentage of married women in the ruling families living less than 50 years decreased steadily, from 48.5 per cent in the sixteenth century to 17.4 per cent in the last half of the nineteenth century. Peller calculated that the survival rates of the white female population in the United States between 1930 and 1939 were more favorable than the survival rates of royal women during the second half of the nineteenth century; but, despite medical advances, the survival rates in that decade for Negro women in the United States were poorer.

In the sixteenth and seventeenth centuries, the risk of maternal death increased with age, but by the latter part of the nineteenth century women 30 to 49 years old had better chances of survival than women 15 to 24 years old. In spite of consistent improvement in mortality rates over the 400 years, mortality among the younger mothers continued to be high (Table 1). Peller (664) concluded that the heavy, elaborate court costumes (in which even children were dressed), which confined and restricted the body, the lack of outdoor exercise and play, the excesses of social life, and the demands of court society upon young women were detrimental to personal hygiene and the natural, healthy development of the female body. The greatest number of marriages occurred among women 15 to 24 years old, and the data show improvement in mortality from the age of 24 years—presumably, environmental and social conditions of young matrons were less injurious.

During the four centuries maternal mortality rates probably were much higher for the European population at large, with social, economic, and medical levels far

TABLE 1

ANNUAL MORTALITY RATES OF WOMEN OF RULING FAMILIES OF EUROPE (664)

(in per cent)

Age in years	Married in				
	1500–1599	1600–1699	1700–1799	1800–1849	1850–1899
–19	1.2	0.20	1.53	1.29	2.52
20–24	1.4	1.13	2.25	1.54	1.62
25–29	1.9	1.73	1.70	1.10	0.68
30–34	1.5	2.07	1.55	1.47	0.72
35–39	2.3	2.25	1.35	1.58	0.43
40–44	2.9	2.78	1.41	1.11	0.70
45–49	3.6	2.37	1.97	1.05	0.54

lower than those of royalty. The notable exception was in mortality among mothers 15 to 24 years old, in whom the more sensible clothing and customs of the lower classes permitted a better chance for health and survival of mother and child. However, Mussey (613) repeated Zückert's comments in 1767 on pregnancy and diet, which included a contrast between the strong, healthy peasant class and ". . . city dwellers and those in the upper classes with weakly bodies and stomachs, tender sensitive nerves who commonly eat anything their appetite demands . . . this is the more dangerous to pregnant women who have no work and exercise. . . . It is a great pity [moderation] does not please those who concede absolute power to their senses."

Apparently most of the maternal deaths occurred during childbirth and the period immediately following, although Peller (664) included all deaths within two months after pregnancy was terminated. Abortion was not considered in the study. From the sixteenth century to the second half of the nineteenth century, puerperal deaths did not fall below two per 100 deliveries, apparently a favorable rate for those times. Peller (664) notes Struyck's report that among almost 2,000 mothers living in Broek between 1654 and 1742, 2.5 per cent died in the first postpartum month. Peller also

points out that in obstetrical wards mortality rates of 7 to 9 per cent dropped after the reforms of Semmelweis had been accepted to as low as 0.3 per cent in the late nineteenth century. After 1849, the maternal death rate in royal families per 100 deliveries decreased to 1.47. For the same half-century, however, maternal mortality was about 0.5 per cent among the general population in England, making the incidence for royalty high in comparison.

In progressive countries such as Norway and Sweden, the general death rate for women in the first half of the nineteenth century was below that of the royal families. Norwegian records from 1801 to 1805 and Swedish records from 1816 to 1840 showed that, per 100 women between ages 20 and 30, the mortality rates were 0.8 and 0.6 per cent respectively, and for the groups 30 to 40, 1.15 and 0.9 per cent respectively. Peller (664) pointed out that the first English records, from 1841 to 1850, showed mortality rates in the royal families for age groups 15 to 19 and 20 to 24 years were, respectively, one and one-half and one and two-thirds times the prevailing English rates for the same age groups, but above 25 years the difference between rates for the population at large and the ruling families was very small.

Not until the twentieth century were maternal mortality statistics available from most countries of the world. The first vital statistics for the United States (295) were published in 1850 but, although the plan was to obtain such data at each decennial population census, the methods used and the data gathered were neither complete nor accurate. In 1900, ten states, some large cities, and Washington, D. C., established a death registration area and, in 1915, a birth registration area. By 1933 all of the states were included. Causes of death are classified according to the *International List of Causes of Death* which is revised every 10 years. Extensive changes in the classification of causes for maternal mortality (listed as "puerperal causes") make comparisons difficult (295). Information for the decade between 1933 and 1943 is computed on the basis of both 1929 and 1938 classifications.

Maternal mortality rates per 1,000 live births in 1940 are available for 47 countries of the world (617). Ceylon and Chile reported the highest rates, 16.1 and 8.1 per 1,000 live births, respectively. Official records for India were not available, but the estimate was as many as 20 maternal deaths in 1,000 births. In spite of incomplete registration and lack of medical certification of death, maternal mortality rates in other South American countries were high: for example, in Colombia, 7.5 per 1,000 live births; cities of Brazil, 7.4; Peru, 6.9; and Mexico, 5.4. The United States, Belgium, and the towns of Egypt had median maternal mortality rates of 3.8. Switzerland had a rate of 3.4. Low rates were given for: Japan (proper), Denmark, and the Netherlands, 2.4; Italy and Sweden, 2.2; Iceland and Norway, 2.0; and France, 1.8. For 23 countries (Table 2) decreased maternal mortality rates were reported for the years 1920 to 1940 except in the Netherlands, Hungary, and Chile. The largest decrease was 62 per cent for France; the smallest, 11 per cent, was noted for Denmark, which might be expected since those countries most progressive in 1920 would show smaller reductions than others.

While in 1940 the United States occupied a median position with respect to international maternal mortality rates, during the 1920's and 1930's the records did not compare favorably with those of countries with similar social, economic, and medical

standards. Many authors, defending the data for the United States, pointed out the differences in method of collecting and tabulating information. In 1931, the Department of Labor studied the comparability of maternal mortality rates for foreign countries with those of the United States. Tandy (854) reported that samples of every type and combination of United States death certificates were sent to 24 countries, 16 of which cooperated by assigning the deaths on the sample certificates to either puerperal or non-puerperal causes, according to the method prevailing in

TABLE 2

PERCENTAGE CHANGES IN MATERNAL AND INFANT MORTALITY RATES FOR 23 COUNTRIES: 1920–1940 (617)

Rank order		Percentage change in maternal mortality rate	Percentage change in infant mortality rate
1	France*	−61.7	−7.1
2	New Zealand (except Maoris)	−55.4	−41.2
3	United States*	−52.5	−45.3
4	Union of South Africa (Europeans)	−50.0†	−44.4
5	Switzerland	−41.4	−45.2
6	Spain	−40.0	−33.9
7	Northern Ireland	−39.1	−8.5
8	Belgium*	−37.7	−10.6
9	England and Wales	−37.2	−30.0
10	Japan	−31.4	−45.8
11	Canada*	−31.4†	−41.2†
12	Scotland	−29.0	−15.2
13	Ireland	−24.5	−15.4
14	Norway	−23.1	−32.8
15	Italy*	−21.4	−18.9
16	Uruguay	−20.6	−25.6
17	Sweden	−18.5	−38.1
18	Australia (except aboriginals)	−18.0	−44.9
19	Iceland	−13.0‡	−56.6
20	Denmark	−11.1	−44.4
21	Netherlands	0	−46.6
22	Hungary	+6.5	−32.6
23	Chile	+8.0	−17.5

* Registration area not strictly comparable between years.
† 1921–1941.
‡ 1921–1940.

that country. Denmark assigned the greatest number of deaths to puerperal causes, and Australia, the Netherlands, New Zealand, and Scotland, in which methods of assignment were known to be similar to those used in the United States, also classified greater numbers of deaths as puerperal than did the United States. Tandy stated that rates for the United States computed by the method used in each country "... are in every instance except Scotland in excess of and are in five instances more than double the official rates of the countries themselves. No matter what method of procedure is used, the United States retains an exceedingly high rate as compared with other countries."

The trend of maternal mortality from 1915 to 1946 is shown in Figure 1. Since 1933, when for the first time all 48 states were included in the registrations, maternal mortality in the United States has declined consistently. From 1933 to 1943 (295) maternal mortality declined 60.4 per cent, from 6.2 deaths from pregnancy and childbirth per 1,000 live births in 1933 to 2.4 deaths per 1,000 births in 1943.

In general, during and immediately after both the First and Second World Wars, maternal mortality increased sharply, reflecting the effects upon mothers of malnutrition, poor housing, epidemics, and unstable social and economic conditions. After each war, the rates decreased, reverting to the pre-war levels except in Great Britain and the United States, where maternal mortality had continued to decline throughout the war. Partial explanations have been found in the food rationing system in England, which produced improvement in the nutritional status of mothers, and the Emergency Maternal and Infant Care program in the United States, which made better prenatal and hospital delivery available to many mothers.

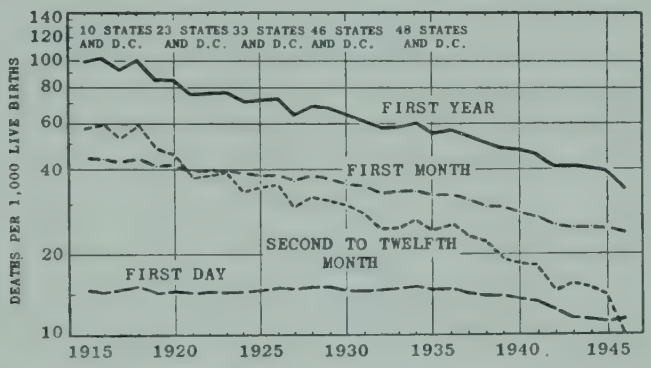

FIG. 1. MATERNAL MORTALITY RATES, UNITED STATES EXPANDING BIRTH-REGISTRATION AREA, 1915–46

War-time statistics for the United States (83) show that during the years 1942 through 1944 there were 20,833 maternal deaths and 8,538,656 live births, 2.4 per 1,000 live births, while the rates for preceding periods were 3.6 for 1939 through 1941 and 5.0 for 1936 through 1938. In 1944, the maternal mortality rate, 2.3, was 6.9 per cent lower than the 1943 rate, 2.4. Considering the continuously high level of maternal mortality found by Peller, maternal mortality rates in the United States for 1947 (Table 3) are dramatic proof of social and medical progress, emphasizing that in childbearing after physical maturity, youth is the mother's best ally. Women 20 to 24 years old had the lowest mortality rate, 0.8, and under 15 and above 30 years group averages were higher than the mean for the year. With a maternal mortality rate in 1947 of 1.3 per 1,000 live births, the United States has gained a favorable position among the countries of the world in the crusade to wipe out maternal mortality from puerperal causes.

Despite the progress in reduction of the over-all mortality rates for the country, regional discrepancies, not only in maternal mortality but also in standards and opportunities for care, point out opportunities for further reduction of both maternal and infant death rates. Maternal mortality rates generally are highest in states with populations of low average economic and educational status, especially in the rural

areas. In the majority of the southern United States the level of medical care is characteristically low. Urban areas, notwithstanding crowding and slum problems, tend to have lower maternal mortality rates, owing to higher average standards of education, nutrition, and medical care and to higher incidence of hospital deliveries.

In 1933 (295), 24 states had maternal mortality rates above 5.9 per 1,000 live births. Florida headed the list with 11.5 and the lowest rate, 4.3, was for Idaho. In 1943, the median rate for the country was 2.2 per 1,000 live births. New Mexico, with a mixed population and poor standards of living, was highest with 4.7 deaths while in Oregon and Minnesota only 1.5 mothers died per 1,000 live births. Michigan, (580) a midwestern state with a population approximately two-thirds urban and one-third rural, demonstrated the possibilities of an aggressive health program by reducing maternal mortality from 5.5 in 1933 to 1.9 per 1,000 live births in 1943.

In 1943 (21) 17 states were below the national average of 72 per cent for hospital births: 819,000 babies were born outside hospitals, and 204,000 babies were born without the help of a physician. A total of 4,500 mothers died from toxemia and infection; most of these deaths could and should have been prevented. In 21 states maternal mortality rates were below the national level. Seven thousand mothers died in childbirth, of whom 5,000 were white and 2,000 were Negro, and for 21 white mothers dying of puerperal causes, 51 Negro mothers died—more than twice as many. The need for better care of Negro mothers and the reduction in maternal mortality which would result from lowering the rate for Negro mothers to that for white mothers was pointed out by Gooch (295).

Maternal Deaths Per 1,000 Live Births

	Total	White	Negro	Other
1933	6.2	5.6	10.0	7.6
1943	2.4	2.1	5.1	4.5
Per cent change.....	−60.4	−62.6	−48.7	−41.5

Gooch (295) stated: "The fact that the rate for Negro women in 1943 was more than twice that of white women should point to ways of further reducing the total maternal mortality. If in 1943 the maternal mortality rate for Negroes had been reduced by a half but the number of both white and negro births and the mortality rate for whites had remained unchanged, the rate for both races would be reduced more than 10 per cent."

Williams (978) emphasized that high maternal mortality rates for Negroes are found in both the northern and southern sections of the United States. In 1935, before the Social Security Act became effective, the total Negro rate per 1,000 live births was 9.5, the total white rate, 5.3. Since 1935 benefits from this legislation have accrued to both races, but in unequal proportions. In 1943 the Negro rate was 5.1 and the white rate was 2.1, 46 and 60 per cent decreases, respectively. According to Williams, in 1931 the Negro puerperal death rates were 45 per cent higher than the white rates in both Georgia and Mississippi, and in 1943 were 74 and 100 per cent above the white rate in each state, respectively. In 1943 the non-white puerperal

death rate for Michigan was 159 per cent higher than the white rate, and in New Jersey the non-white rate was 138 per cent higher than the white rate.

In 1944 (22), the level of maternal mortality among the non-white population of the United States lagged 15 years behind that for the remaining population, and in 1947 (619), the rate for non-whites was three times that for the white race, 3.3 versus 1.1 per 1,000 live births. Regional rates (575) for white and non-white mothers also showed wide discrepancies: New England, 0.9 and 3.2, respectively; eastern south-central states, 1.6 and 3.9; and the mountain region, 1.2 and 4.5. Although the average maternal mortality rate in the United States was low in 1947 (575), geographic variations indicate the scope of problems remaining. For the white population in the Pacific and New England regions, a rate of 0.9 prevailed, while in the eastern south-central states, the mortality rate was 1.6 and the hospitaliza-

TABLE 3
DEATHS FROM PUERPERAL CAUSES AND MATERNAL MORTALITY RATES, BY AGE: UNITED STATES, 1947 (619)

(Rates per 1,000 live births in each specified group)

Age of mother	Total deaths	Rate
Total*	4,978	1.3
10 to 14 years	21	4.7
15 to 19 years	488	1.1
20 to 24 years	1,013	0.8
25 to 29 years	1,118	1.1
30 to 34 years	1,040	1.7
35 to 39 years	871	2.9
40 to 44 years	375	4.8
45 to 49 years	48	9.0
50 years and over	3	15.2

* Figures for age "Not stated" included in the total, but not distributed among the specified age groups.

tion rate was 55 per cent (for Negro women alone, only 23 per cent, emphasizing the high number of deliveries by midwives) in contrast to 98 per cent in the Pacific states.

Regardless of reductions in maternal mortality which can be cited to show how many mothers do not die in comparison with earlier periods owing to continuous advances in economic and social status and medical care, thousands of maternal deaths continue to occur each year. The incidences of deaths from hemorrhage, toxemia, and infections, the three major causes of maternal deaths, shift with area depending on the race distribution, economic and social status, and political administration of the population and on the level of prenatal and obstetric practice. Information is limited regarding abortion (96) as a factor in maternal mortality rates, although many cases of infection seen in hospitals are actually the end products of abortions. Little is known regarding the incidence of "successful" abortions or their effect on the outcome of subsequent pregnancies.

In the decade between 1933 and 1943 infection continued to be the first cause of maternal death in the United States:

Maternal Deaths per 1,000 Live Births (295)

	All causes	Infections	Toxemias	All other
1933	6.2	2.4	1.5	2.4
1943	2.4	0.9	0.6	1.0
Per cent change.....	−60.4	−62.6	−57.8	−59.9

In those years, however, maternal deaths from both infection and toxemia were tremendously reduced. The discovery of chemotherapy during this time contributed

TABLE 4

NUMBER OF DEATHS AND PERCENTAGE DISTRIBUTION, BY TIME OF DELIVERY, FOR EACH CAUSE: UNITED STATES, 1940 (123)

Death in relation to time of delivery	Maternal deaths*							
	Infection		Toxemias		Hemorrhage, trauma, or shock		Other and unspecified causes	
	Number	Per cent distribution	Number	Per cent distribution	Number	Per cent distribution	Number	Per cent distribution
Total.....	3,626	100	2,250	100	2,058	100	942	100
Ectopic gestation.....	85	2	—	—	307	15	—	—
During or after abortion†.....	1,334	37	80	3	109	5	159	17
Before delivery.....	—	—	939	42	55	3	304	32
During or after childbirth‡.....	2,207	61	1,231	55	1,587	77	479	51

* Deaths in the continental United States that were due directly to diseases of pregnancy, childbirth, and the puerperium (numbers 140–150 of the *International List of Causes of Death*, 1938 revision).

† Abortion is defined as the termination of a uterine pregnancy prior to 7 lunar months (28 weeks) of gestation.

‡ Childbirth is defined as the termination of a uterine pregnancy at 7 months (28 weeks) or more of gestation.

greatly to the decline in deaths from infection, and during that time hospitals inaugurated more effective regulations to achieve asepsis in obstetric service, blood for transfusions became available in greater quantities and over larger areas, prenatal care was improved, nutritional factors gained recognition and became pre- and postnatal considerations, and obstetric techniques were vastly improved (295).

In 1940 (123), 8,876 mothers died in the United States, 3.8 per 1,000 live births. The distribution by cause shows that 41 per cent died of infection, 25 per cent of toxemias, 23 per cent of hemorrhage, trauma or shock, and 11 per cent of unspecified causes. Percentage distribution by time of delivery (Table 4) shows that 4 per cent of the mothers died in connection with ectopic gestation, 19 per cent during or after abortion, 15 per cent before delivery, and 62 per cent during or after childbirth.

In 1944 (83) infection was responsible for 33 per cent of 6,369 maternal deaths (Table 5) and hemorrhage, trauma or shock for 30 per cent. Toxemias accounted

for 25 per cent, 1,607 maternal deaths, of which 800 were eclampsia and 390 were albuminuria and nephritis. In 740 instances (12 per cent) death certificates did not provide satisfactory information, indicating the need for clarification of the certificate and more detailed statements by physicians. Of the total deaths connected with all phases of reproduction and childbearing, 64.6 per cent occurred during or after delivery. Infection caused almost three-quarters of the deaths associated with abortion, and hemorrhage caused more than four-fifths of deaths during ectopic gestation.

TABLE 5

MATERNAL DEATHS* FROM EACH CAUSE AND BY TIME OF DEATH IN RELATION TO DELIVERY: UNITED STATES, 1944 (83)

Cause of death	Total	Ectopic gestation	During or after abortion	Before delivery	During or after childbirth
	Number				
All causes	6,369	345	996	915	4,113
Infection	2,125	63	701	—	1,361
Toxemias	1,607	—	67	589	951
Eclampsia	800	—	—	306	494
Albuminuria and nephritis	390	—	—	135	255
Other toxemias	417	—	67	148	202
Hemorrhage, trauma, or shock	1,897	282	115	69	1,431
Other and unspecified causes	740	—	113	257	370
	Per cent				
All causes	100	100	100	100	100
Infection	33	18	70	—	33
Toxemias	25	—	7	64	23
Eclampsia	13	—	—	33	12
Albuminuria and nephritis	6	—	—	15	6
Other toxemias	6	—	7	16	5
Hemorrhage, trauma, or shock	30	82	12	8	35
Other and unspecified causes	12	—	11	28	9

* Deaths due directly to diseases of pregnancy, childbirth, and the puerperium.

Comparison of causes of maternal mortality in various states and regions reveal patterns similar to those for all the United States. In 1944, (83) the lowest rates were in the northern Rocky Mountain area, the highest in the South; deaths connected with abortions were proportionately high in the District of Columbia, Kansas, Montana, and Nevada; in Utah, North Dakota, New Hampshire, and Nebraska, deaths connected with abortions were low. Williams (978) points out, among the economic and social conditions which contribute to the high maternal mortality rates among the Negroes in the South, the inter-related factors of illegitimacy, abortion, and infection; the large, unplanned families, existing on a low economic

level; and the prevalence of syphilis, with its influence on the stillbirth rate, (for the Negro twice that of the white) and consequent danger to the mother because it is known that the risk of maternal mortality is much higher when a child is born dead than alive. The Negroes' low standard of living and ignorance of nutrition is linked with greater morbidity and potential mortality: anemia with characteristic hemorrhagic complications, and rickets with pelvic deformity and resultant dystocia, are common. Hypertensive disease, occurring three times as frequently as in the white race, and the heavy salt pork diet predispose to the toxemias of pregnancy which, compared with other regions, are especially high in the South. The rank of maternal mortality causes in a northern state like Michigan in 1948 (580) emphasizes the low toxemia rate: other and unspecified causes, 7 per cent; toxemias, 23 per cent; infection, 26 per cent; hemorrhage, trauma or shock accounting for the greatest proportion, 44 per cent.

The principle causes of infant mortality are prematurity, anoxia, birth injuries, and malformations. A stillbirth or a premature birth, coupled with a complicated pregnancy, poor nutritional status, or unskillful delivery may affect a mother's health; but, from the pediatric point of view, the problems of stillbirth, prematurity, birth injuries, and fatal or badly-damaging neonatal anoxia are all attributable to the maternal situation. (The problem of malformations still requires comprehensive investigation.) Even though an infant survives birth, early mortality (within the first hours, day, week or month when the heaviest toll occurs) from the four main causes may still be thought of as directly related to maternal mortality. After the infant is delivered, the cord cut, and the independent organism has lived through the first critical month, certain causes of infant mortality can more readily be attributed to exogenous factors: respiratory infections (pneumonia and influenza), gastrointestinal disturbances (infant diarrhea, enteritis, and dysentery), and epidemic and communicable diseases.

Information pertaining to infant mortality is far more extensive than data concerning maternal mortality, although an element of inaccuracy is involved in infant mortality statistics owing to the confusion in classifying stillbirths, and inconsistencies in birth and death registration procedures. All over the world customs and religious observances govern methods of registration and prevalence in recording certain causes. Infants who are stillborn may, to insure baptism be registered as "neonatal" deaths; on the other hand, in some countries, a child who dies soon after birth may be registered as stillborn or as a miscarriage, to avoid using both birth and death certificates.

Maternal mortality is in a great measure the direct result of obstetrics and medical care, but infant mortality rates after the first week of life, in which maternal nutrition and ante-partum care are the important elements for sound, healthy babies, more truly reflect the economic advantages of the mothers.

Peller (664) surveyed 8,466 births in ruling families from 1500 to 1930. In this group, infant mortality[1] in the sixteenth century was 193 per 1,000 infants born alive,

[1] "Infant mortality"—deaths before one year of age of infants born alive; "neonatal mortality"—infant deaths in the first seven days; "stillbirth rates"—"number of all born dead except abortions and miscarriages, per 100 born either alive or dead."

and increased to 246 per 1,000 for the next century (Table 6), evidently owing to the generalized lowering of personal and community hygiene standards characteristic of the seventeenth century. (Maternal mortality during that century did not show effects of poorer hygiene). Infant mortality in ruling families diminished to 153 in the eighteenth century; to 96 and 41, respectively, in the first and second halves of the nineteenth century; and to 8 per 1,000 infants born alive in the first 30 years of the present century. Deaths after the first month of life seem to have been fewer from gastro-intestinal disturbances than from respiratory infections. The royal families did not have the summer peak in infant mortality which was characteristic of the general population in the seventeenth and eighteenth centuries (664).

Infant mortality was studied (664) as early as the second part of the seventeenth century, but because so many babies died during their first year of life, little information was segregated on occurrence of death during the first week. Deaths from the second to twelfth month of life were two, three, or four times those of the neonatal

TABLE 6

INFANT MORTALITY AND STILLBIRTHS IN RULING FAMILIES (664)

Time of parents' marriage	Total born	Total stillbirths	Total born alive	Deaths per 1,000 live births				
				1st day	1st week	Whole 1st month	2nd to 12th month	Entire 1st year
1500–1599	1903	21	1882	(27)*	89	98	95†	193
1600–1699	2716	88	2628	(33)*	75	96	150‡	246
1700–1799	1862	55	1807	29	47	60	93	153
1800–1849	791	23	768	23	34	50	46	96
1850–1899	820	9	811	6	12	17	23	41
1900–1930	374	1	373	3	5	5	3	8

* Recorded without sufficient data for exact classification according to age.

† Includes 2.7% of infants who died within the first year without the exact age recorded.

‡ Includes 1.5% of infants who died within the first year without the exact age recorded.

period plus stillbirth rates until the present century. In Vienna from 1752 to 1754 the rate for stillbirths plus neonatal deaths was 9.7 per cent: the infant death rate for the second week to the end of the first year was 33.1. The comparable rates for white infants in the United States in 1940 were 5.0 and 2.1 per cent, respectively. For the first week, exclusive of stillbirths, the infant mortality rates were: Vienna, 7.5 per cent; United States, 2.2 per cent.

Records for the ruling families (Table 6) in the sixteenth century often mentioned only that the infant "died young" or "soon after birth." Actually, death may have occurred during labor. From 1600 to 1849 (664) the stillbirth rate per 1,000 live births was rather stable: 32, 30, and 29; from 1850 to 1899 the rate dropped to 11; and from 1900 to 1930 dropped again to 3. Peller emphasized that the stillbirth rate from 1850 on among the royal families was lower than stillbirth rates reported by some leading hospitals recently, and believed that progress in medical care could not, alone, be cited as the reason for reduction in stillbirths. Peller attributed the reduction to modification of court habits and customs, which after 1850 permitted pregnant

women to live less strenuously. However, Mussey (613) quotes Burnett of London, who apparently had another opinion of the upper classes and in 1880 wrote: "The child of the well-fed, well-worked, cheerful, happy woman living in a sunlit, airy habitation, is at birth the finest specimen of its kind. On the other hand, what a miserable sight do the newborn babies of our courts and alleys, and of the pampered, tight-laced, high-heeled, lazy, lounging, carriage-possessing women of the high classes present: The extremes meet, the poor, blanched creature, half-starved, overworked, shut in some close sunless dwelling brings forth her fruit very like that of the pale-faced, over-fed, under-worked, sofa-loving sister of the mansion and of the palace."

Royal records did not list precisely the gestational age of infants, but knowing that prematurity causes the greatest percentage of stillbirths and deaths in the first week of life we may conclude that before 1850 the incidence of premature births must have been high and that decreased numbers of premature births after this date were in large part responsible for the reduction in mortality soon after delivery. After 1850 there was also a significant decrease in deaths in the first month of life (Table 6), similar to the reductions in stillbirth and neonatal rates.

Peller (664) cited statistics on stillbirths and "neonatal mortality"[2] gathered in Philadelphia (912), Chicago (360, 683), and New York (719, 289) which showed stillbirth rates, exclusive of abortions, between 2.3 and 3.0 per cent, and neonatal mortality of 2.1 and 3.2 per cent, figures two and one-half to three and one-half times the 1.85 rate for ruling families between 1850 and 1930.

Peller (664) concluded that, if the royal families were able to make such a remarkable reduction in the loss of infants, modern pessimism over the ultimate reduction of early mortality, especially prematurity, is definitely unjustified. Peller believed that factors of heredity, constitution, and family (which, because of intermarriage, were stronger than usual among royal families) played only a minor role in the incidence of prematurity, and emphasized that full-term development of the fetus may be regarded largely as a result of maintaining suitable environmental conditions for the mother. "Apparently incidence of prematurity is not a matter of wealth or privilege, but of the degree of relaxation and physical and mental rest (664)."

Infant mortality figures of the ruling families (Table 6) compared with statistics of various countries show that the rates among royalty in the eighteenth century were from 90 to 160 years ahead of the general populations (664). Not until the 1840's did Sweden match the royal rate of 15.3 per cent for the previous century. A similarly low rate did not occur until the 1860's in England, the 1890's in Switzerland, and 1910 to 1915 in Italy and Germany. Later comparisons are not quite so marked. The royal level of 9.6 per cent between 1800 and 1845 was met in the 1870's by New Zealand, the 1890's by Sweden and Norway; in 1910 to 1915 by England, Holland, and Switzerland; in 1916 by the white population in the United States; in the 1920's by France, Belgium, and Germany; in 1930 by the Negro population in the United States, and in 1939 by Italy. In the second half of the nineteenth century, various European countries showed a range between 85 and 214 per 1,000 live births, and

[2] Peller did not give definitions of this term as used in the American studies.

some central European countries were even as high as 484; during this period the ruling families succeeded in lowering their infant mortality rate to 41 per 1,000, a figure reached and surpassed in the twentieth century by New Zealand between 1921 and 1925 and the Netherlands and Sweden between 1935 and 1938.

In the survey of maternal and infant mortality since the Renaissance, Peller's conclusions may possibly be limited and not so entirely applicable to the contemporary situation, because in his study he was unable to evaluate many factors. The sample surveyed was small, there were no doctors then as we know them, records on infants regarding the time of death were neither precise nor complete by present standards.

In the twentieth century total infant mortality has declined steadily as hygiene and medicine have advanced; however, much less progress has been made in lowering the neonatal death rate. Yerushalmy (998), comparing neonatal mortality with death rates of older infants, found the variation among countries to be much smaller for mortality in the first month of life than for deaths in the next eleven following. The total mortality rates in Italy and the United States in 1938 were 106.3 and 51.0 per 1,000 live births, respectively. In neonatal mortality there was little difference between the two countries; actually, during the first day of life the mortality rate was higher in the United States than in Italy, but at the end of the twelve months the Italian rate was almost 6 times the American rate. Neonatal deaths are higher in proportion to all infant deaths in countries with low total mortality rates, representing about two-thirds of the total infant mortality, whereas in countries with higher total mortality rates less than one-fourth are neonatal.

The infant mortality rates of 20 selected countries (617) for 1912 and 1937, the years before the World Wars, are shown in Table 7. Data were not available for South American countries between 1912 and 1919, but in 1937 Chile and the Dominican Republic, respectively, had the highest and lowest rates, 240.7 and 45.8; in 1944, however, infant deaths in Chile fell to 180.8 and in the Dominican Republic rose to 79.7 per 1,000 live births. In the European area, the tiny islands Malta and Gozo consistently had the highest rate, reaching 345.2 in 1942. Bulgaria and other Balkan countries have consistently shown high infant mortality rates, emphasizing that in that area of large peasant population and predominance of rural, agricultural life, opportunities for improvement exist similar to those revealed by records for the southern sections of the United States.

The percentage changes in maternal and infant mortality rates of selected countries between 1920 and 1940 given in Table 2 show that changes in maternal and infant rates were not parallel.

Infant mortality rates for the Union of South Africa are usually separated for Europeans and non-Europeans, but for the latter cannot be considered accurate since infant death registration is incomplete and irregular. In 1937 the rate for non-Europeans in 9 principal towns was given as 239.5 (617) but in 1947 a report (283) stated that in one of the native territories only 500 of 1,000 live births lived to be 18 years old, and that of the 500 who died, 300 died before the end of the second year of life. Deplorable conditions exist also in Brazil, where records are incomplete except for principal cities, in 21 of which the rate in 1937 was 205.2 (617), but

estimates are that in the vast interior regions, as many as 500 infants die per 1,000 live births (129).

TABLE 7

INFANT MORTALITY RATES IN SELECTED COUNTRIES*

(Exclusive of stillbirths. Rates are the number of deaths reported under 1 year of age per 1,000 live births)

Country†	1912	1937
Chile	—	240.7
Dominican Republic	—	45.8
United States	—	54.4
India (British)	207.9	161.7
Japan (proper)	154.2	105.8
Palestine	—	152.8
England & Wales	94.8	57.6
Germany	147.4	64.4
Greece	—	122.2
Iceland	66.7	32.1
Italy	128.1	108.8
Malta & Gozo	268.1	242.7
Netherlands	87.0	38.1
Belgium	126.7	82.8
France	105.9	65.4
Norway	67.2	42.0
Sweden	70.9	45.2
Switzerland	93.8	46.7
Australia	71.7	38.1
New Zealand		
(except Maoris)	51.2	31.2
(Maoris)	—	92.2

* Selected from data (617) for 46 countries during the years 1912 through 1919, and 1937 through 1944.

† Rates for the Dominican Republic and India for 1937 are not to be considered a measure of the true level of infant mortality because of the irregularity and incompleteness of the infant death registration. Data for India for 1912 are for a registration area which includes about 98 per cent of the total British territory and 75 per cent of India proper. (Statistics include Burma.) Data for India for 1937 are for a registration area which includes almost 100 per cent of total British territory, and 76 per cent of India proper. Data for Palestine for 1937 are for "settled" population, excluding Nomadic Bedouins. (In 1939, rate was 107.5; 1942, 122.4; 1944, 87.2.) Data for Germany for 1912 include data for Alsace-Lorraine and those for 1937 are for Altreich, i.e., territory of 1937, including the Saar. Data for Malta and Gozo for 1912 are for year ending March 31. Data for the Netherlands for 1912 exclude, in addition to stillbirths, infants born alive but dying before registration of birth. Data for Australia exclude aboriginals.

Of the Asiatic countries which kept records in 1912 (617), the Straits Settlements, Malaya, had the highest rate, 282.5. For the same countries in 1937, the registered area of Burma had the highest rate, 203.0, with 105.8 and 105.1, respectively, for Japan (proper) and the Netherlands East Indies (Java and Mandura plus the Europeans in the Outer Provinces). Records are not available for the U.S.S.R. since the

revolution of 1917, although statistics from certain satellite countries such as Romania and Bulgaria were available until their inclusion in the Russian sphere of influence before, during, or after the Second World War.

Dramatic changes in infant mortality rates are evident in data for countries which have been recording vital statistics since the beginning of the century. Advances in medical science, education of the public, and development of public health services are mirrored in the reduction of infant deaths in Sweden and New Zealand. The total infant mortality of Sweden (9) declined from 78.1 per 1,000 live births during the five year period 1906–1910 to 31.0 between 1941 and 1944. A reduction in neonatal mortality during the first week from nearly 19.0 per 1,000 live births in 1940 to 14.5 in 1942 has been attributed to the Swedish prenatal supervision system established in 1940. Infant mortality decrease in New Zealand from 69.6 per 1,000 live births in 1906–1910 (excepting the Maoris) to 26.1 in 1946 has been attributed to the work of The Plunket Society (186).

Prior to the Second World War, available sources all show reductions in total infant mortality rates but with wide variations among the countries. Gillespie (282) states that in 1938 and 1939 infant mortality varied from 300 to 37 per 1,000 live births. Burma and the Netherlands East Indies reported the highest rate, 300, which was two to three times that of other Far Eastern countries, although statistics from India, China, and Indo-China were not included. The Balkan states also had high rates, while the United States, the Netherlands, and Norway had the lowest rates, 45, 38, and 37, respectively, for the last prewar years.

During World War II the total infant mortality in many countries and cities remained favorable; however, some countries showed tremendous rises. According to the Epidemiological Reports of the Health Division of UNRRA (915, 916), if infant health organizations continue to function, infant mortality will usually be less affected from curtailed food supplies than will the mortality of children and grown-ups; but if these health services collapse during the war or are inadequate, the infant mortality rate increases. In countries where civic health services were maintained, infant mortality was affected little by the war itself (in fact, sometimes improved because of vaccines, DDT, new drugs, and even superior service). But at the end of the war, infant mortality rates all over Europe rose drastically, a direct result of postwar epidemics throughout the continent.

Infant mortality rates for 1939 and 1945 compare (916) favorably for Great Britain, southern Italy (where the war ended earlier than elsewhere), Spain (where their Civil War ended in 1939), and the Scandinavian countries. The rate for England, which before the war was 60 per 1,000 live births, ranged during the war years from 46 to 59. The German prewar rate was not exceeded until 1942, and in France the greatest infant mortality occurred in 1940. (In France infants born alive but dying before the birth is registered are not included in the rate based on live births.) In Norway, infant mortality remained low, dropping in 1943 and 1944 to 35.4 and 36.7 respectively, per 1,000 live births. However, in the Netherlands, infant mortality increased three-fold over the 1939 level (916). From March, 1941, to the end of March, 1946, (917), over 200,000 cases of diphtheria were recorded, in contrast to 7,000 cases listed during the previous five years. In eastern France and central Italy,

areas of heavy military engagement, the infant mortality rate more than doubled (916). In Athens and Piraeus, Greece, infant mortality per 1,000 live births rose from 90 in 1940 to 231 in 1942, but in age groups over 40 the mortality increase was four-fold (916) showing that the lack of food, especially during the severe famine from November, 1941, to February, 1942, affected infants less than adults.

Infant mortality rates in some large cities of the world are shown for both the prewar and war years in Table 8. UNRRA reports also cite unofficial information and reports. For instance, in November, 1945, the infant death rate was reported

TABLE 8

INFANT MORTALITY IN SELECTED LARGE CITIES OF THE WORLD (916)

(Deaths under 1 year per 1,000 live births)

City	Months covered	1945	1944	1943	1939	Index*
Copenhagen	12	45	41	32	34	1.3
Oslo	12	26	34	30	30	0.9
Stockholm	11	24	23	23	32	0.8
16 Scottish Cities	12	62	76	73	76	0.8
126 English Cities	12	54	52	58	52	1.0
Dublin	12	110	109	128	90	1.2
Strassbourg	11	117	46	67	50	2.3
Amsterdam	8	105	38	36	32	3.3
Brussels	11	72	64	53	56	1.3
Liège	9	111	65	51	73	1.5
Nantes	6	135	79	75	46	2.9
Paris	10	91	60	57	61	1.5
Bologna	6	278	118	89	60	4.6
Florence	6	117	91	66	56	2.1
Rome	6	103	121	89	71	1.5
Madrid	8	85	75	77	157	0.5
Johannesburg†	12	—	43	53	52	—
Buenos Aires†	12	—	—	41	45	—
Toronto†	12	—	36	36	43	—
New York	12	—	31	30	37	—
Bombay†	12	—	203	195	—	—
Auckland†	12	—	—	35	29	—

* 1945 rate in units of 1939.

† 1945, (915).

to be 145 per 1,000 in Hamburg, 2.9 times the 1938 rate. For Berlin, during the five weeks ending October 12, 1945, it was 231 per 1,000 live births, and in Vienna during the summer of 1945, the rate given was 325 per 1,000. In the midst of Europe progressive countries with low prewar infant mortality rates suddenly showed rates previously found only in the Far East. Widespread epidemics, diphtheria, typhus, influenza, were cited as causes and in all the cities shown, 1945 rates were above those of the war years (Table 8).

This world-wide pattern of progressive decline in total infant mortality and almost static neonatal mortality rates extended also to the United States, in which from

1915 to 1946 mortality the first day of life continues in a horizontal line in contrast to downward curves of infant mortality at other ages (Figure 2). In 1933, a total of 120,887 infants died during the first year of life, in 1943, only 118,484, the rate dropping from 58.1 to 40.4 per 1,000 live births, a reduction of 30 per cent (295):

Infant Deaths per 1,000 Live Births

	Total	White	Negro	Other
1933	58.1	52.8	85.4	127.5
1943	40.4	37.5	61.5	84.6
Per cent change.....	−30.5	−29.0	−28.0	−33.6

In 1933, 2,000,000 babies were born in the United States and in 1943, 3,000,000 (21). Although during this decade the number of babies born in hospitals increased

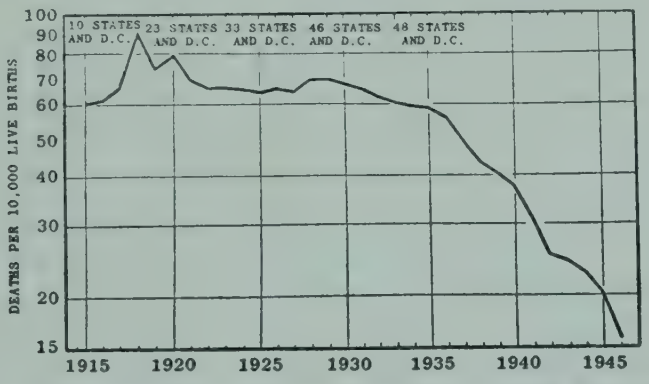

FIG. 2. INFANT MORTALITY RATES, BY AGE, UNITED STATES EXPANDING BIRTH-REGISTRATION AREA, 1915–46

106 per cent (21), five times as many babies died in the first year of life (118,000) in 1943 as there were servicemen killed in action that year (24,000).

Incidence of infant mortality appeared in patterns similar to those for maternal mortality, with the southern and Rocky Mountain states highest, the northwestern and northeastern states far lower. In both 1933 and 1943, New Mexico had the highest infant mortality rate, 136.1 and 89.3, respectively, per 1,000 live births; however, over the decade a reduction of almost one-third occurred. In 1933, Washington State had the lowest infant mortality rate, 38.8, and in 1943, Connecticut was lowest with 29.4. The greatest reduction, 43 per cent (60.0 to 35.4) was made by North Dakota, and the least reduction, 10 per cent (38.8 to 34.9) by Washington (97). In 1943, 23 states were less successful than the nation as a whole in saving babies' lives, showing rates above the national rate of 40 infant deaths per 1,000 live births, and the risk of death for Negro babies was much greater than that for white babies: 62 to 38 (21). In 1946, the total infant mortality rate was 33.8 for the country, and only nine states had rates of 40.0 or above (15). The non-white rate was 49.5, and in five states more than 100 of every 1,000 non-white infants died before they were one year of age (15). In 1947, the infant mortality rate under one year

for non-white infants was 48.5 per 1,000 live births, and for white infants, 30.1 per 1,000 live births. After the first few days of life the relative differences between mortality in the two races were greater than in the period immediately following birth (619).

Mortality in the first month of life continues to be an unsolved problem. Yerushalmy (998) pointed out that "it has often been stated that infant mortality is one of the most sensitive indices of environmental and health conditions. Upon closer investigation, it is found that this statement is true only for mortality during the second to the twelfth month of life, while neonatal mortality is not strongly correlated with external environmental factors." He stated that, conservatively, 1,225 conceptions are needed to allow 1,000 babies to live beyond the first year of life. This "reproductive wastage" of 225 is made up of about 150 abortions ("expulsion, either spontaneous or induced, of pre-viable fetus") of which at least one-half are induced; 30 stillbirths ("death of a viable fetus during pregnancy or before birth is completed"); and 45 infants born alive who die, termed infant mortality. In addition, three mothers are lost.

Yerushalmy (998) concluded that the causes behind neonatal death are related to "physical" aspects and factors in parents and infants rather than to outside influences. The mortality of male infants is 25 per cent higher than that for female infants. Yerushalmy cited investigations (995, 996) showing a higher risk for mothers younger than 20 and older than 30, that the age of the father affects the offspring, and that high mortality is associated with high parities, while the death rates for second and third births are far lower. He pointed out that there appears to be an optimum time between pregnancies, and noted that the premature rate as well as the neonatal mortality rate goes up if the interval between pregnancies is either too short or long. In contrast to Peller's conclusions, Yerushalmy believed that there is a "familial tendency" to stillbirths, prematures, and neonatal mortality, and for a mother who has lost a previous child, later infants incur a risk double that of later infants of mothers whose previous children have lived. Yerushalmy (998) concluded, "These associations suggest that genetic factors may be at least partly responsible for neonatal mortality and premature birth (998)."

It is generally accepted that, despite the confusion in recording and assembling figures, stillbirths should be excluded from infant mortality statistics, although the causes contributing to each may well be identical. Because of the combination of stillbirth and neonatal mortality figures in many countries, it is difficult to survey the incidence of stillbirths except in countries such as England, Scotland, Norway, and the United States, from which statistics on stillbirths alone are available. Areas of low maternal mortality show correspondingly low stillbirth rates.

In 1922, the first year for which figures were available in the United States, the stillbirth rate for fetuses born after five or more months of gestation was 39.4 per 1,000 live births. By 1935, the rate had decreased only 10 per cent, but by 1945 the rate had dropped to 23.9, almost 40 per cent less than the 1922 figure. The rates for white and non-white groups in 1945 were 21.4 and 42.0, respectively (685).

The Metropolitan Life Insurance Company (574) reported in 1947 that "although the ratio of stillbirths to live births has been declining in recent years, the number of children born dead (about 65,000) is still more than 10 times the number of women

who die from puerperal causes in a year." Stillbirth rates per 1,000 live births listed for the white population of 47 states between 1940 and 1944 showed an average for all ages of 24.4. Under 15 years of age, the rate was 32.9, but only 21.3 for the group 15 to 19 years old. The lowest incidence, 18.5, was in the 20 to 24 year age group. For succeeding ages, the rates increased, reaching 80.4 for women 45 and over, four times the rate for women in their early twenties (574).

Norway, notwithstanding its consistently low total infant mortality rate, has had a relatively high stillbirth rate. Per 1,000 live births, from 1901 to 1925, the rate was 23.9, and from 1931 to 1935, 24.9. Over a 20-year period (1916 through 1935) the stillbirths occurred in lower proportions between May and September, which has been attributed to seasonal variation in sunshine and availability of fresh fruits and vegetables in Norway (885, 901).

During the war stillbirth rates increased in many countries, but in others decreased. Baird (30) noted a striking reduction in stillbirth rates throughout England, Wales, and Scotland. The English rate fell from 38 per 1,000 in 1939 to a provisional 28 in 1944; the Scottish rate for the same years fell from 42 to 32. Comparison of records for 1940 and 1944 emphasized a decrease in the group of stillbirths due to unknown causes and to trauma and toxemia during pregnancy. Mortality in the group classified "cause unknown" (33 per cent of the total) was reduced nearly 50 per cent. Baird believed the explanation for these reductions was the improved nutritional status of women in the lower classes resulting from the food rationing system.

Drillien (201) studied 7,599 births occurring between 1942 and 1945 in Simpson Memorial Pavilion, Edinburgh. The series included 373 stillbirths (177 premature, 165 mature or "postmature"), 4.9 per cent. A fetus was considered to be a stillbirth if the estimated length of gestation was 28 weeks or longer, regardless of birth weight. In both premature and mature babies the primary cause of stillbirth was found to be asphyxia (53 cases) or asphyxia plus hemorrhagic and pneumonic complications (28 cases). Congenital defect was listed in 71 cases; subdural hemorrhages accounted for 11 stillbirths; and erythroblastosis fetalis, "other causes," and congenital syphilis were responsible for 6, 5, and 2 fatalities, respectively. Intrauterine death before labor, with maceration, occurred in 75 cases. Autopsy was not performed in 122 instances. When the stillbirths were evaluated in relation to complications of pregnancy, the high incidence of hydramnios occurring with congenital defect (nearly always anencephalus) was noted; the toxemia rate was twice as high as in the survivor group and higher than that associated with any other cause of stillbirth.

In discussing fetal and neonatal deaths, Mengert (570) states: "Approximately 4 per cent of all fetuses and newborn children reaching a size and development compatible with extrauterine existence die before, during, or soon after birth.... Of these, almost one-third die in utero and one-fifth perish during the birth process. About one-half are born alive, but succumb within the first few postnatal days or weeks."

The major causes of death among infants in the European countries and America are prematurity, birth injury, asphyxia or anoxia, and congenital malformations. In considering combined stillbirths and neonatal deaths (the first ten days) Potter and Dieckmann (686) wrote: "When the total loss of life is considered, both that occurring before and after birth, anoxia caused by interference with the passage of

fetal blood into the placenta, or failure of the fetal blood to obtain oxygen from the placenta is responsible for more deaths than any other condition. The principal pathologic state causing such a disturbance is premature detachment of the placenta."

Potter and Adair (685) hold the opinion that it is only justified to term "asphyxial" or "anoxic" those deaths in which the primary causative factor lies outside the fetus. Such causes are divided into three groups: (1) "those due to qualitative changes in the maternal blood" (such as severe maternal anemia, and anesthetic agents such as nitrous oxide); (2) "those due to interference with oxygenation of the fetal blood in the placenta" (for instance, conditions of either abruptio placentae or placenta previa); and (3) "those due to inability of blood to pass from the placenta to the fetus" (prolapse, knots, entanglements, and abnormalities of the cord). It is suggested by these authors that atelectasis and asphyxia (which results from atelectasis) should be used only as descriptive words for infants who have suffered from primary oxygen deficiency in utero, who were born alive but died after delivery. If antenatal anoxia has not been present, "asphyxia" should not be used as a descriptive term, since failure to establish respiration has occurred as the result of a factor existing before birth, such as abnormalities of the central nervous system or the lung, or mechanical compression of the lungs.

Prematurity ranks second as a cause of infant deaths. A baby weighing under 2,500 gm. is generally accepted as premature regardless of length of gestation. Brown and co-workers (85) suggest that different criteria should be used in judging full-term Negro and white infants. Negro babies are naturally smaller, and, even at term, often fall into the artificial weight division of prematurity, although they may be vigorous, healthy infants.

Between 3 and 11 per cent of all live-born infants are premature. The incidence is higher in unmarried than married mothers; with multiple births; with complications of pregnancy such as toxemias, chronic nephritis, syphilis and placenta previa; with serious illness, tuberculosis, and heart disease; with "disturbances in the ovum" (312) which result in monstrosities; with surgery for the mother; and with women with records of habitual abortion. Mengert (570) pointed out that the causes of deaths reported from "immaturity" relate to pregnancy and not to labor, and noted increased incidence of premature labor with toxemia, multiple pregnancy, ante-partum hemorrhage, and infection, and cited records from four American hospitals:

Incidence of Premature Termination of Pregnancy (570)

	Deliveries, number	Years	Incidence, per cent
New York Hospital (165)	31,900	1932–43	2.95*
Philadelphia Lying-in (914)	33,668	1930–44	8.8†
Cincinnati Gen. Hosp. (85)	13,526	—	10.9†
Parkland Hosp., Dallas (571)	4,123	1944–46	11.3*

* Infants weigh 1,500–2,499 gms.; † infants weigh less than 2,500 gms.

Parkland Hospital, which had the highest incidence of prematurity, serves indigent patients almost entirely, of whom three-fourths are Negro or Mexican.

Birth injuries, or "birth trauma" which is the term Potter and Adair (685) use to include anything exclusive of oxygen deficiency which affects the fetus adversely during labor or delivery, are in large part attributable to poor delivery technique or to the lack of competent medical service. The incidence of birth injury is increased when version or traction is necessary, when high forceps are employed, when complicated deliveries are handled by midwives, and when hospital facilities are not available.

Hemorrhage is one of the most serious consequences of birth injury. According to Greenhill (312) cerebral hemorrhage accounts for many fetal deaths and for almost one-half of the fatalities among premature babies. Because cerebral hemorrhage and asphyxia have occurred in a large proportion of deaths among premature babies, Greenhill believes prematurity, cerebral hemorrhage, and asphyxia must be considered together (312).

Malformations also are an important cause of infant mortality. Surgical treatment is frequently effectual in the correction of anomalies such as pyloric stenosis, Tetralogy of Fallot, clubfoot, and cleft palate, but in monstrous births survival is usually impossible. Murphy (611), studying the occurrence of congenital malformations among siblings, pointed out a repetitive incidence of both unusual and more common defects among sisters and brothers within a family; that the birth of a malformed child is usually related to a long period of relative sterility; that the birth of the malformed child is often preceded and followed by a stillbirth, abortion, or premature; but that environmental influences (health of parents, illegitimacy, interval between pregnancies, diet, economic status, among many listed) have not been proven to directly affect malformations. He states: "The observations which have been made during the course of the present investigation lead to the general conclusion that gross, human, congenital malformations arise solely from influences which affect the germ cells prior to fertilization. No evidence is available to indicate that they result from factors which operate for the first time after fertilization has taken place (611)." However, the occurrence of malformations as results of rubella (and, in animals from other virus infections) is well-established.

In addition to prematurity, anoxia, birth injury, and malformations, fatalities also occur from congenital and infectious diseases. For diseases attributed to Rh-factor incompatability, figures are incomplete, widely scattered in the literature, and difficult to evaluate. Potter and Dieckmann (686) found that erythroblastosis fetalis was the cause of death in one of every 400 deliveries, and that most of the deaths from this disease occurred during the first three days of life. Of all deliveries at the Chicago Lying-In Hospital between 1941 and 1946, there were 44 deaths, a rate per 1,000 live births of 2.5. The same hospital (685) reported 147 pregnancies (exclusive of abortions) in 86 women following delivery of a first child with erythroblastosis: three children were Rh-negative and normal; 12 were Rh-positive and survived; and 132 were Rh-positive and either died or were stillborn.

There is a great need for further studies based on autopsies rather than on clinical findings alone, to determine the causes of deaths during the neonatal period. Greenhill (312) cites from the Holland and Lane-Claypon (1926) records based on autopsies and clinical records of 1,673 "dead births" and "neonatal deaths" in London, Glasgow

Liverpool, Edinburgh, and Cardiff. Cruickshank (156) reported, from autopsies of 800 babies born in the Glasgow Royal Maternity and Women's Hospital who died during the neonatal period, that conditions associated with delivery ("asphyxia neonatorum," congenital atelectasis, prematurity, or birth injury) were responsible for the death of 540, or 68 per cent. Of the 540 (140 mature, 400 premature) 244, or 45 per cent, lived less than one day. Death was attributed to infection acquired before, during, or after delivery in 238, or 30 per cent, of the infants. Congenital anomalies were responsible for only 22 deaths and syphilis caused less than one per cent.

Potter (680) cited records from the New York Lying-In and Sloan Hospital for Women, and the Chicago Lying-In Hospital, where 1,000 and 1,173 fetal and neonatal

TABLE 9

CAUSE OF INFANT AND FETAL DEATH (680)

Cause of death	New York Lying-In Hospital and Sloan Hospital for women, per cent	Chicago Lying-In Hospital, per cent
Anoxia	19.8	28.7
Primary prematurity	18.5	14.4
Congenital malformation	14.1	11.1
Birth trauma	11.6	13.0
Infections	8.1	4.7
Erythroblastosis	2.8	2.2
Hemorrhagic disease	2.1	0.3
Syphilis	0.6	0.2
Maceration and maternal toxemia	5.2	5.3
Maceration, no toxemia	13.5	11.9
Unknown, not macerated	3.0	6.5
Miscellaneous	0.7	1.7
Total mortality	3.87	4.28
Mortality over 1,000 Gm.	3.52	3.50
Total cases	1,000	1,173
Stillbirths		614
Deaths		559
Duration of Study	1935–1940	1931–1941

deaths, respectively, were studied, about 90 per cent of which were autopsied. The etiological factors in deaths were similar in both groups (Table 9).

To evaluate infant mortality during the first year by time of occurrence emphasizes the unequal distribution of deaths and the unequal opportunity for their reduction. Greenhill (312) states, "We know that the first 15 minutes after birth is the most dangerous period of life." By far the greatest number of infant deaths occur on or under the first day of life; but all factors regarding the death of infants under one month should be studied, if any reduction is to be achieved in this area where, in spite of improved obstetrical skill and increased hospital deliveries, little progress has occurred in any country during the past half-century.

Infant mortality rates in the United States by age, from under 1 day through 11 months, from 1915 to 1947 are shown in Table 10. The continuation of high

rates for infant deaths under 1 day, as well as under 1 month, may be compared with the effective reduction in mortality over 1 month of age throughout the years selected. Mortality among the infants who survive the first few days of life has declined more rapidly than mortality among the newborn. Since 1915, the mortality rates for infants 7 to 13 days old have decreased 71.7 per cent, and for infants 9 to 11 months old, 89.5 per cent. Mortality among infants was reduced only 28.7 per cent for infants under 1 day, 55.2 per cent for infants 3 to 6 days old. Since 1915 the proportion between infants dying under 1 week of age and number of infants dying in the first year has almost doubled, increasing from 30 to 59 per cent (619).

TABLE 10

INFANT MORTALITY RATES BY AGE: BIRTH-REGISTRATION STATES, FOR SELECTED YEARS (619)

(Exclusive of stillbirths. Rates per 1,000 live births)

Age	1947	1945	1940	1935	1930	1925	1920	1915
UNDER 1 YEAR	32.2	38.3	47.0	55.7	64.6	71.7	85.8	99.9
Under 1 day	10.7	11.2	13.9	15.0	15.0	15.0	14.8	15.0
1 day	3.4	3.3	3.5	3.7	4.2	4.2	4.6	4.9
2 days	2.1	2.1	2.2	2.4	2.9	3.2	3.4	3.5
3 to 6 days	3.0	3.1	3.6	4.4	5.1	5.8	6.4	6.7
7 to 13 days	1.7	2.1	2.4	3.1	3.9	4.4	5.4	6.0
14 to 20 days	1.0	1.3	1.6	2.0	2.5	2.9	3.8	4.6
21 to 29 days	0.9	1.2	1.4	1.8	2.1	2.3	3.1	3.7
Under 1 month	22.8	24.3	28.8	32.4	35.7	37.8	41.5	44.4
1 month	2.0	2.8	3.5	4.4	5.3	5.8	7.3	9.0
2 months	1.6	2.2	2.9	3.5	4.2	4.6	5.7	7.6
3 to 5 months	3.0	4.5	5.9	7.1	8.8	10.3	13.1	16.9
6 to 8 months	1.7	2.7	3.6	4.8	6.2	7.4	10.0	12.5
9 to 11 months	1.0	1.6	2.4	3.5	4.6	5.8	8.3	9.5

During the decade from 1933 to 1943, the percentage changes in the age of occurrence of infant deaths (295) were:

	First year	First month	First day
1933	58.1	34.0	15.1
1943	40.4	24.7	11.6
Per cent change	−30.5	−27.4	−23.2

The incidence of the three principal causes of infant and neonatal mortality decreased little between 1940 and 1946 (Table 11), although those deaths from infectious causes, influenza, and pneumonia, were reduced from 7.4 to 3.8, and those from diarrhea, enteritis, and ulcerations of the intestines dropped from 3.5 to 1.7 during those years. Of 111,127 infant deaths in 1944, Brombacher (83) states that

68,996 were neonatal (under 1 month) and that approximately one-half of these infants died during the first day. The neonatal mortality in 1944 was 24.7 deaths per 1,000 live births; the mortality rate for infants less than a day old was 11.5 per 1,000 live births, and for those between 1 day and 1 month, 13.2. "Prenatal and natal causes," including premature birth, congenital malformations and debility, syphilis, and other diseases of the first year of life (deaths from infectious and communicable diseases excluded) were responsible for 67,713 or 60.9 per cent of all infant deaths in

TABLE 11

INFANT MORTALITY RATES FOR CERTAIN CAUSES: IN UNITED STATES 1940–1946 (618)

(Exclusive of stillbirths. Rates are the number of deaths under 1 year per 1,000 live births)

Cause of death	1946	1945	1944	1943	1942	1941	1940
All causes	33.8	38.3	39.8	40.4	40.4	45.3	47.0
Pneumonia (all forms), and influenza	3.8	5.3	5.6	6.2	5.7	6.7	7.4
Diarrhea, enteritis, and ulcerations of intestines	1.7	3.0	3.3	3.0	2.8	3.7	3.5
Congenital malformations	4.5	5.0	5.1	4.9	4.9	4.7	4.7
Premature birth	12.1	11.6	11.9	11.8	12.3	13.3	13.7
Injury at birth	3.6	3.6	3.6	3.7	4.1	4.3	4.5
All other causes	8.0	9.9	10.3	10.7	10.6	12.7	13.3

TABLE 12

THE NEONATAL INFANT MORTALITY IN THE CITY OF OSLO SINCE 1900 (905)

Years	Deaths in the 1st year of life per 1,000 live births	Neonatal deaths as percentage of total infant mortality
1900	125	24
1910	93	28
1920	33	44
1930	39	61
1939–1944	30	65
1939–1947*	11.7	83

* Data from a supervised prenatal group of one-fourth of all the mothers and children of Oslo

1944. In deaths under 1 month, equal percentages, 14.5, were attributable to congenital malformations and to birth injuries, including cerebral and other hemorrhages.

In Norway (905), the neonatal mortality rate between 1921 and 1925 was 42.8 per cent of the total infant mortality. In 1900, the neonatal mortality of Oslo was 24 per cent of the total infant mortality, 125 per 1,000 live births; but from 1930 on, as the total infant mortality rate decreased, the relative neonatal mortality as a percentage of the total constantly increased to 60 or 65 per cent (Table 12). In a supervised prenatal group of one-fourth of all the mothers and children of Oslo between 1939 and 1947, of 18 infants dying in the 9-year period, 15, or 9.7 per 1,000 live births died during the first month; only 3 infants, 1.9 per 1,000 live births, succumbed after their first month of life but before they were 1 year old.

Moncrieff (590) showed the trend of neonatal mortality in England and Wales from 1906 to 1944:

Deaths under 4 weeks per 1,000 live births (590)

1906–10	40	1936–40	29
1911–15	39	1941	29
1916–20	37	1942	27
1921–25	33	1943	25
1926–30	32	1944	24
1931–35	31		

Baird (30) also gave mortality figures per 1,000 live births for the first 4 weeks of life: in England from 1938 to 1943, the rates successively were 28.3, 28.3, 29.6, 29.0, 27.2, 25.2; and in Scotland from 1938 to 1944, 35.7, 36.5, 37.2, 39.9, 35.1, 32.9. Both countries recorded increases in rates for 1940 and 1941, but in 1944 the rates were lower than those for 1939. The causes of deaths during the first month of life in England and Wales from 1938 to 1943, expressed as deaths per 1,000 live births, were (30):

Cause of death	1938	1939	1940	1941	1942	1943	1943 as percentage of 1938
Prematurity	13.83	13.65	13.66	13.65	12.80	12.03	86
Congenital malformations	3.85	3.87	4.21	4.07	4.11	3.67	87
Birth injury	2.62	2.70	2.66	2.47	2.49	2.29	95
Congenital debility	1.06	1.05	1.12	1.02	0.83	0.61	57
Enteritis and diarrhea	0.42	0.41	0.59	0.47	0.61	0.53	125
Bronchitis and pneumonia	1.07	1.17	1.52	1.68	1.33	1.33	87
Other causes	5.45	5.42	5.85	5.64	5.06	4.76	89
All causes	28.30	28.27	29.61	29.00	27.23	25.22	

The causes for infant mortality which are of such importance in Europe and the United States are in other areas of the world lost among the critical problems of death from exogenous factors. Where the level of sanitation, public health, and nutrition is low and inadequate food reduces bodily resistance, even without prematurity or other neonatal handicaps, the infant who does survive the difficult process of birth probably does not have, even after the first month, a chance of survival equal to that of infants in the more favored countries. Infectious diseases such as Ekiri, an acute form of diarrhea which causes a high number of infant deaths in Japan (617); infantile beriberi in Far Eastern countries (12,248); infantile pellagra and rickets, amoebiasis, tuberculosis, typhus, and malaria in South Africa (283); and the widespread incidence of dysentery diseases, acute respiratory infection, and tuberculosis in Brazil (129) are all equally important in the problems of infant death, and must be met on the local level.

II

SPECIFIC NUTRITIONAL FACTORS IN MATERNAL AND INFANT HEALTH

Although nutrition is one of the youngest of the sciences, man's interest in the properties of foods and the environmental circumstances by which he was able to sustain life, growth, and reproduction are evidenced in his earliest records. After hundreds of years in which the most able minds speculated regarding processes of nourishment with the limited knowledge provided by their senses, discovery of some of the basic laws of chemistry and physics permitted some progress in understanding the physiology of respiration and digestion in relation to energy exchange and the proximate composition of foods.

The trickles of discovery which in the nineteenth century presaged the Age of Science became foaming torrents soon after 1900. The cycle—knowledge, speculation, theory, research, new knowledge—was repeated with accelerated frequency as man strove prodigiously to understand the functioning of his own body. The accumulation of facts demanded division and realignment of both the fundamental and applied sciences, and previously small areas of interest assumed the stature of separate but interdependent sciences. The concept of food as substance providing protein for muscle-building, minerals for skeletal growth, and carbohydrate and fat for energy has in less than 50 years been expanded by recognition of varying amino acid composition among proteins, of the involvement of over 50 mineral elements in the composition and functioning of body tissues, of the importance of accessory factors in growth, development, and health; of fats as lipids composed of fatty acids, neutral fats, soaps, waxes, sterols, and phosphatides; of fat as bearer of accessory substances; and of the significance of proportionate distribution of food components in the body requirements for them and in its resistance to and recovery from disease.

With the magnificent progress of the twentieth century the horizons of nutrition have receded and future accomplishments in revision and expansion of our knowledge have been projected on the basis of the achievements which have characterized past development. Nutrition is recognized as the prime factor in the propagation of individuals with the maximum potential for physical development and in their maintenance of the best physical status possible throughout life. Thus, the development of healthier, stronger individuals in a healthier, stronger nation must start with better nutrition for mothers (and fathers) before and during pregnancy and during lactation, as well as improved nutrition for infants and children. Improved nutrition of mothers and children, coupled with further advances in medical service and social development inevitably will produce further reductions in maternal and infant mortality. It is the purpose of the following pages to outline the extent and sources of our knowledge of those specific nutrients, the intakes of which are known to determine adequacy of dietary with respect to all requirements, and to point out uncertainties which must be dispelled by further investigation.

Definite antagonisms are known to exist among food constituents: oxalate and

phytates decrease the quantities of calcium, magnesium, and iron available for absorption, and a diet rich in corn increases the need for niacin. The general constituents of the diet undoubtedly play a larger role in determining the exact need of any one nutrient than has been generally realized.

The ingestion of certain drugs may upset the nutritional balance: salicylate seems to increase the excretion of ascorbic acid and interferes with the production of prothrombin. The sulfa drugs not only change the intestinal flora, thus altering absorption, but also they replace paraaminobenzoic acid in certain chemical structures.

Interrelationships between some of the nutrients and the utilization of some of the amino acids also are known to exist; for example, ascorbic acid facilitates the utilization of tyrosine and phenylalanine.

The substitution of compounds related chemically to certain of the constituents of body enzymes renders these enzymes completely ineffective.

The interdependence of the hormones, enzymes, vitamins, and amino acids is becoming more clearly defined, and the trace minerals have been shown to have a major influence on the enzyme system, blood formation, and hormone synthesis. This whole field of interrelation and antagonism of various substances influencing the nutrition of both the mother and the child is still to be explored.

ENERGY VALUE AND PROXIMATE COMPOSITION

Energy: The surface area of a newborn infant is about 15 per cent, but his body weight is only about 5 per cent, that of an adult. Per kilogram of body mass the newborn infant has about 700 square inches of surface, while the adult has only 200. Rubner postulated that the basal metabolism is related to body surface. Benedict and Talbot (49), however, found that heat production during the first day of life is definitely higher than on other days of the first week and averaged 612 calories per square meter per 24 hours at 2 days of age. During muscular activity they found heat production was increased 4 to 211 per cent, averaging 65 per cent, and concluded (48) that metabolism is determined by the active mass of protoplasmic tissue.

Smith (790) states that during the newborn period the average infant produces about 1.7 calories per kilogram per hour and has a total 24-hour basal requirement for food which will yield about 41 calories per kilogram of body weight. To this must be added 30 per cent for bodily activity, 10 per cent for fecal loss, 12 per cent for specific dynamic action, and some growth allowance, which together make the requirement as much as 80 calories per kilogram per day.

Jeans and Marriott (409) state that normal infants, on the average, require 55 calories per kilogram a day for basal metabolism during the first year of life. This is only an approximation, since there is not a perfect correspondence between basal metabolism and body weight, even in infants. They calculate the total average daily energy requirement of an infant to be 115 calories per kilogram, distributed as shown on page 32.

Individual variation in energy requirement is great. An underweight infant, whether premature or not, has a relatively greater food requirement because of larger surface area in relation to weight and of the relatively larger mass of actively functioning tissue, which is the main determinant of energy requirement. Intakes of 200

calories per kilogram of body weight by athreptic infants before a gain in weight occurred have been reported (882). Hypogalactia, which is quite frequent, is a common cause of undernutrition in early infancy. If an infant is quiet a mother may not be aware of low milk flow and continue nursing her baby when she has insufficient milk in her breasts. The infant may develop athrepsia, which may retard the infant's development and in some instances result in permanent damage.

For premature infants Talbot and co-workers (853) assumed the caloric requirement for gain in weight to be considerably higher, up to two and one-half times the basal demand, or about 150 calories per kilogram per 24 hours (70 per pound). Gordon and associates (302), however, concluded that after 2 weeks premature infants showed satisfactory weight gains with 120 calories per kilogram (55 per pound). Premature infants seem to reject fat and to utilize carbohydrate preferably, whereas full-term newborn infants live mainly on stored fat until milk can be digested (409). Most of the enzymes necessary for digestion of various foods seem to be present in a newborn infant, but complex carbohydrates are not split by the enzymes present at that age (790).

	Calories	
	Per kg.	Per lb.
Basal resting metabolism	55	25
Allowance for specific dynamic action	10	4
Allowance for activity	25	10
Allowance for growth	15	7
Allowance for unutilized food	10	6
Total	115	52

Carbohydrate: Carbohydrate is an essential constitutent of the body and is, therefore, necessary for life. Theoretically, however, it is not an essential part of the diet because approximately 60 per cent of the protein intake is convertible to dextrose in the body. Authors agree with Jeans and Marriott (409) that 10 gm. of carbohydrate should be fed per kilogram of body weight in infancy. The breast-fed infant receives this amount from a full breast. In artificial feeding the reduced concentration of lactose in diluted cow's milk may be counter-balanced by adding carbohydrate. Opinions differ and various forms have been advocated: lactose, sucrose, and various forms of starch hydrolysates such as dextrin, maltose, and dextrose. Common sucrose has been found to have the same nutritive value as milk sugar and is easily absorbed from the intestinal tract and digested. It has the advantage of not being laxative, which provides safety in feeding infants with digestive disturbances. The carbohydrate of fruits, largely dextrose and levulose, seems to be utilized very well by infants.

The most-discussed questions concerning carbohydrates are the amounts needed by infants and the age at which infants need additional starch in the diet. In general, starch is incompletely digested by the very young infant and with large intakes some is usually detected in the stools. Except for therapy, to make the feeding thick to

prevent vomiting, for instance, the advantage of adding starch to the diet of an infant under 6 months of age is not great. Starch is colloidal and may have some value in diarrheal disturbances in infancy.

Infant formulas in common use some years ago tended to contain too much carbohydrate because weight gain from such feeding is rapid, owing to simultaneous water retention. Administration of a diet high in carbohydrates but deficient in proteins, minerals, and vitamins may produce rapidly gaining, pale, flabby, waterlogged infants, usually with varying degrees of anemia and lowered resistance to infections. Most of the symptoms described by Czerny and Keller (159) under "exudative diathesis" were probably results of this type of feeding. The symptom complex is not caused by any toxic effect of carbohydrates, as was thought 20 to 30 years ago, but by the deficiencies of protein, minerals, and vitamins in mixtures of diluted milk containing a high percentage of carbohydrate. Disturbances of carbohydrate metabolism seem to be results of overfeeding more often than of underfeeding. Carbohydrates are inexpensive, readily available, easy to prepare, weight-producing, and therefore, to the layman, desirable.

Carbohydrates seem to be easily absorbed by the newborn infant, at least insofar as the mono- and disaccharides are concerned. As the blood sugar of the newborn is rather low, 40 to 100 mg. per 100 ml. (790), the requirement for carbohydrate is evidently high. At birth the infant is using carbohydrate almost exclusively for heat production, evidently an extension of fetal conditions. Good results have been reported from giving, during the newborn period, even larger amounts of carbohydrates than are contained in breast milk. A simple diffusion of dextrose through the placenta seems not to occur, for the mother's blood is always higher in glucose than is the newborn infant's.

Fat: Fat can be oxidized completely to carbon dioxide and water in the human body, but by the adult only in amounts which approximate 2.5 gm. daily per kilogram of body weight. Above this intake, unoxidized residues are excreted as ketone bodies. The maximum rate of fat oxidation by infants is unknown, but it is well below that of adults. The younger and smaller the infant, the less efficient fat oxidation seems to be and ketosis develops more easily. Fat may to a large extent be replaced by carbohydrate as a source of energy. Certain constituents of fat such as those which are carriers of the fat-soluble vitamins are essential for growth. In animal experiments some unsaturated fatty acids, such as linoleic and arachidonic acids have been found to be essential in averting skin lesions. It is believed that arachidonic, linoleic, and linolenic acids cannot be synthesized by the human body.

Fat provides about one-half of the calories available from human and from cow's milk. The fat of undiluted cow's milk contains greater amounts of the esters of the fatty acids of lower molecular weights, which in weak and sick infants may have an irritating effect, producing vomiting and diarrhea. Cow's milk fat contains only about half as much of the unsaturated higher molecular weight acids (409) which include the so-called "essential fatty acids."

Evans (241) found that dietary fat affects the composition of cow's milk fat. It would be expected that the composition of dietary fat also influences the fat in human milk. For a normal full-term infant slight variations in the relative lipid

composition do not make any appreciable difference. In sick, prematurely born, and weak infants fat utilization seems to be poor and their formulas must be low in fat and high in protein and carbohydrate. Because of the larger amounts of casein and calcium in cow's milk, its fat forms insoluble calcium soaps in the intestine and therefore is not so well utilized as the fat of human milk. Under usual conditions this does not seem significant.

Formerly, a newborn infant generally was considered to have a rather high fat absorption, up to 95 per cent (603), but later studies of young infants (374) indicate lower fat absorptions by younger infants. In premature infants fat absorption is lower than in full-term infants. Tidwell and associates (872) found absorptions by premature infants of from 58 to 83 per cent for various forms of fat. Gordon and McNamara (303) found an absorption from cow's milk of 75 per cent of the fat by full-term infants but of only 53 per cent by premature infants. The concentration of fat in the blood of a newborn baby is low in comparison with that of the mother (73, 348, 723, 784) but is doubled by the second week of life, which probably is an expression of increased transport of fat substances by the blood.

Protein: Proteins, with their component amino acids, are the main structural units of protoplasm and their importance is reflected in a diversity of body functions—osmotic relations, blood clotting, antibody production, oxygen transport, enzyme and hormone production, muscular contraction, pigment formation, and detoxicating mechanism. Proteins are organic aggregates of amino acids which when absorbed are converted to structural proteins and in part de-aminated to provide energy, with excretion in the urine of non-protein nitrogen. The ratio between anabolized and catabolized amino acid fractions depends on various factors: quality and quantity of ingested proteins, total caloric intake, nutritional state of the individual.

The biological value of a protein depends on its amino acid composition. Some of these acids the organism may synthesize; those which it cannot manufacture are essential amino acids, or as defined by Rose (720), "indispensable" dietary components. For adult man the indispensable amino acids are: tryptophan, lysine, methionine, threonine, phenylalanine, leucine, isoleucine, and valine. Histidine and arginine, until recently included among the essential amino acids, have been shown not to be essential for adult human beings. Glycine, alanine, cystine, serine, tyrosine, norleucine, aspartic acid, glutamic acid, hydroxyglutamic acid, proline, hydroxyproline, and citrulline may be synthesized in the human body. Common protein foodstuffs of animal origin contain all of the essential amino acids in high concentrations. Most vegetable proteins are lower in biological value (usually low in lysine) but are valuable adjuvants in dietary supplementation. The essential amino acid contents of some common foods used in infant feeding are given in Table 13.

Sillevis (779) and Bar (37) who were among the first to report studies of pregnant women, in the early 1900's found good positive balances in pregnant women. Slonaker (785, 786) tested the effect of different levels of protein in the diets of pregnant rats and found that, for fertility and for success in pregnancy, a diet containing 14 per cent protein was best and one with a high protein content, 26 per cent, was least successful. Macomber (511) found 20 per cent protein in the diet of pregnant rats superior to all lower levels and calculated that this level for rats represented 100 to

125 grams daily for women. Guilbert and Goss (323) found oestrus absent or irregular when protein in the diet was below 7.5 to 8 per cent.

Theoretical protein requirements in pregnancy may be estimated from analyses of fetuses and their adnexa and from metabolism studies. Figure 3 shows the accumulation of nitrogen in the human fetus during gestation on the basis of 92 fetuses for which analyses were published, accompanied by length measurements from which comparable fetal ages could be determined (415). The gravid maternal organism must supply protein not only for the fetus but also for the placenta, the uterus, and the mammary glands. At term the fetus composes 5 to 7 per cent of the mother's weight. When the adnexa and mammae are included the maternal weight at term is increased by 10 to 20 per cent according to Harding (336) and Lusk (497). Hunscher

TABLE 13

ESSENTIAL AMINO ACIDS IN PROTEINS OF SOME FOODS USED BY INFANTS AND CHILDREN (IN PER CENT) (472)

(Calculated to 16.0 per cent Nitrogen)

	Milk*		Egg	Meat	Fish	Wheat		Rice
	Lactalbumin	Casein				Flour	Bread	Polished
Arginine	3.5	4.1	7.0	7.2	5.6	3.9	3.5	7.2
Histidine	2.0	2.5	2.4	2.1	1.9	2.2	2.3	1.5
Isoleucine	4.5	6.5	5.3	3.4		3.7	2.8	5.1
Leucine	12.2	12.1	19.0	12.1		12.0	11.2	7.7
Lysine	8.0	6.9	6.0	7.6	6.8	1.9	2.8	3.2
Methionine	2.8	3.5	3.5	3.2	3.4	3.0	2.3	3.4
Phenylalanine	5.6	5.2	5.2	4.5	4.5	5.5	5.1	6.3
Threonine	5.3	3.9	4.9	5.3	4.4	2.7	2.8	3.9
Tryptophan	2.3	1.8	1.6	1.2	1.3	0.8	1.3	1.3
Valine	4.0	7.0	4.4	3.4		3.4	3.1	6.4

* The protein content of human milk averages 1.25 per cent (0.2 per cent nitrogen), the casein fraction comprising 0.5 per cent and the whey proteins (chiefly lactalbumin) 0.75 per cent. Corresponding values for cow's milk are 3.5 per cent protein (0.56 per cent nitrogen), 2.8 per cent casein, and 0.7 per cent whey proteins.

and co-workers (389) and Wilson (986) stated that the average fetus at term contains 70 gm. of nitrogen. Pratt *et al.* (687) found 5.7 to 11.9 gm. in placentae from nine women. Jackson (401) calculated 17 to 18 gm. for the placenta and 1 gm. for the amniotic fluids and the membranes, a total nitrogen content of about 89 gm. To this amount must be added 17 gm. nitrogen for the growth of the mammary glands and 39 gm. for the enlargement of the uterus, according to Macy and Hunscher (525), making the total nitrogen requirement in excess of maintenance during pregnancy about 140 gm., or 870 gm. of protein.

According to Hunscher and Macy (389, 525) and Coons and co-workers (143, 144) the maternal organism tends to store nitrogen in excess of the theoretically calculated requirement. Under favorable circumstances 200 to 400 gm. of nitrogen are stored in excess of the requirement for the fetus and accessory structures, represent-

ing 1250 to 2500 gm. of protein. The nitrogen balance becomes negative abruptly just before term, resulting in a loss of nitrogen from the maternal body during parturition and the postpartum period, as well as from postpartum bleeding, placental extrusion, and changes in the uterus and other pelvic organs. The nitrogen emitted in breast milk amounts to 1 to 1.5 gm. daily; thus, the reserve accumulated during pregnancy is a natural mechanism providing in advance for the large losses during delivery, puerperium, and lactation.

Sontag and Wines (808) were unable to demonstrate a relationship between weight, height, and ossification of infants at birth and the protein intakes of 203 mothers during pregnancy. They did not, however, conclude that protein intake has no effect on the status of the infant at birth, but rather that protein intake must fall below the levels current in the group they studied before such an effect is clearly demonstrable.

Hummel and co-workers (387) found nitrogen retentions variable among individual women, depending upon previous nutrition and general health. They found the

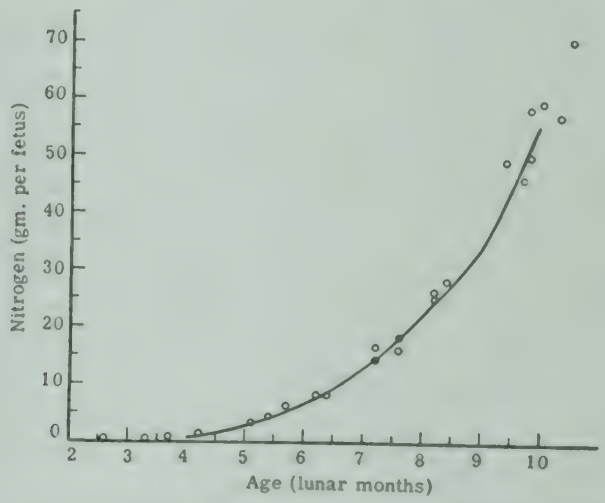

FIG. 3. NITROGEN CONTENT OF THE HUMAN FETUS

nitrogen retention of a pregnant woman with an unsatisfactory nutritional background for 6 years was only 86 gm., whereas a pregnant woman with a satisfactory nutritional background over the same interval of time retained 196 gm. This rather surprising finding might have been the result of damaged body cells being unable to retain large amounts of nitrogen owing to previous long-standing undernutrition. The authors emphasized that the maternal nutritional state and physiological constitution are important and should always be considered when interpreting studies of dietary requirements in pregnancy. In one woman (862) a mean daily nitrogen intake of 19 gm. for 135 days preceding delivery at term was accompanied by an average daily retention of over 3 gm.

Despite high nitrogen balances, the extra-maternal demands for protein produce a physiologic lowering of plasma proteins from preconception levels of 7.0 gm. per 100 ml. to 6.2 gm. by the sixth month of pregnancy (472). Electrophoretic determinations (148) have shown total plasma protein to be 13 per cent lower in the third trimester of pregnancy than mean values for non-pregnant women. Through delivery, plasma concentration trends were consistently downward for albumin and gamma

globulin and upward for the $alpha_1$, $alpha_2$, beta, and phi (fibrinogen) globulins. The level of blood protein has been reported to return to normal about the seventh postpartum day, but electrophoretic patterns (148) show significant variations from non-pregnant values for proteins in blood samples obtained 5 to 6 days postpartum. Mean values for blood samples obtained 6 to 12 weeks postpartum were significantly different from non-pregnant levels in $alpha_1$ and beta globulin components on the basis of 100 gm. of protein and in albumin and $alpha_1$ globulin on the basis of 100 ml. of plasma.

During pregnancy 2 gm. of protein has been recommended per kilogram of body weight. If this amount might be justified in some instances, in others it may be unnecessarily high in the early stages of pregnancy. The Food and Nutrition Board of the National Research Council (257) recommended a daily intake of 85 gm. of protein in the latter half of pregnancy, about 1.5 gm. per kilogram of body weight.

The impression has been that an excess of protein or of particular proteins may be harmful in pregnancy. Theobald (862, 863, 864, 865) studied high protein levels in diets of pregnant bitches and found that metabolism products of meat protein produced changes in the liver tissue, lowering liver function. High meat consumption during human pregnancy was followed by a condition corresponding to intoxication. McIlroy (515) also considered the high intakes of meat during pregnancy undesirable because toxic products are liberated during the catabolism of the protein.

Levine (472) stated that little support remained for the belief that high protein intakes unrelated to preexisting hypertension and cardiorenal disease predispose to toxemias of pregnancy. In preeclampsia and eclampsia hypoproteinemia combined with edema is frequent. Plass and Matthew (667) in 1926 pointed out that in the general lowering of blood protein in pregnant women it was the albumin fraction especially which was diminished. Eastman (211) calculated the average albumin-globulin ratios in the blood of normal non-pregnant women, normal gravidas, and women with eclampsia or preeclampsia to be 1.7, 1.6, and 1.3, respectively. With persistent albuminuria he found that total serum protein may fall to between 4.0 and 5.0 gm. per 100 ml. of blood. Such an alteration decreases the osmotic pressure and, according to Eastman, probably plays an important role in the production of the edema associated with toxemias of pregnancy.

Strauss and Castle (828) in 1932 pointed to the necessity of a protein intake high enough to prevent anemia in pregnancy. Strauss (825) reported the osmotic pressure of the plasma proteins to be lowered in eclampsia (175 mm. of water) in relation to the value for normal pregnant women (258 mm. of water). The dietary histories of 20 toxemic pregnant women showed that low protein intake, resulting in lowered osmotic pressure of the plasma proteins, was essential in the pathogenesis of pregnancy toxemia and the conclusion was affirmed in a later publication (472).

Dodge and Frost (197) found an increased intake of protein was tolerated well by patients with mild toxemia and produced a diminishing of objective and subjective symptoms. The relationship between low-protein intake and poor hemoglobin formation in dogs, earlier reported by Whipple (966), was emphasized by Bibb (56). In 216 pregnancies studied by Burke and associates (100), 28 cases of toxemia occurred: 44 per cent among patients with "poor, or very poor" diets and 8 per cent among those whose diets were "fair," whereas among those with diets rated "good" or "ex-

cellent" not a single case developed. A direct relationship to protein intake could not be found. Arnell and co-workers (25) found a higher incidence of toxemia among patients eating low-protein diets than among those eating liberal amounts of protein. Holmes (371) found the incidence of toxemia in 350 primiparas and 350 multiparas ingesting low-protein diets was twice as great as that in similar groups receiving high-protein diets.

During 1941 to 1944 the food ration in Norway allowed pregnant women about 1 gm. of protein daily per kilogram of body weight. During these years meat protein was nearly absent from diets and the main sources were fish and milk. At the Municipal Health Center of Oslo (903), 1025 pregnant women were supervised during the years of war. Nearly all were given 40 to 50 gm. of brewer's yeast per day throughout pregnancy. During the first 2 years, before food rationing, albuminuria was present in 12 and 19 per cent, respectively, whereas the percentage in the 4 following war years ranged from 2 to 7. Eclampsia did not occur during this time, and the maternal mortality was zero. These results evidently were related to the constant supervision and the rationing program During the months of acute hunger in Holland during 1945 the individual's ration was 750 to 900 calories and 35 to 40 gm. of protein per day. On this ration the incidence of toxemia at the midwifery school of Rotterdam fell to about half that occurring in the same institution during the pre- and post-hunger periods. Dieckmann (191), however, did not find any relation between toxemia and low-protein diet. There are possibilities of other factors influencing the relationship of protein intake to toxemia during gestation. Theobald (185, 862–65) has pointed to calcium and thiamine as such factors and Mellanby (563) supported him in this view. It seems likely that the interrelationship among the constituents of diets representing low levels of total food intake is an important factor in the nutritional status of the people subsisting on such diets.

For human mothers the usual percentage of protein in the diet is 14 to 20 per cent of the total food intake. Recent studies (100, 212, 213, 214, 215, 833) in Canada and the United States on the nitrogen content of the diet in relation to the condition of the fetus and the infant have provided interesting figures. Of 216 women studied during pregnancy by Burke and co-workers (100), only 10 per cent consumed diets containing the amount of protein (85 gm.) recommended by the Food and Nutrition Board of the National Research Council (257): 68 per cent of the diets contained less than 70 gm. and 38 per cent less than 55 gm. of protein daily. A significant relationship (100) was found between the protein content of the mother's diet during pregnancy and the weight and length of her infant at birth (Table 14). Stuart (832) found also a relationship between the osseous development in infants at birth and the protein content of their mothers' diets during pregnancy.

Arnell and co-workers (25) found that, of 400 pregnant mothers in New Orleans, 18 per cent took less than 42.5 gm. of protein daily, i.e., less than half the recommended allowance, and 63 per cent took less than 70 gm. daily. Williams and Fralin (980) showed that only 13 per cent of mothers in Philadelphia were ingesting the recommended daily allowance. Sydenham (849) considered the amenorrheal state noted in British mothers in Hong Kong during World War II probably was caused by malnutrition, particularly deficiency of protein. Smith's (792) finding of amenor-

rhea in 60 per cent of the women of menstrual age in the large cities of Holland during the last hunger period there may be related to the deficiency of protein in the diet. It is probably the anterior pituitary gonadotrophic hormone which is influenced by the lack of protein, thus producing cessation of the menstrual cycle.

Positive nitrogen balances are usually found by the end of the first week of life (58) and in premature infants retention of nitrogen is especially high (292, 410, 457, 739). Premature infants 2 to 5 weeks old may retain 250 mg. of nitrogen per kilogram of body weight per day, twice the retention of full-term infants under comparable conditions. The protein from cow's milk is utilized equally as well as that from human milk, and with the concentration in the formula adjusted to levels of calories and protein equivalent to human milk, as much as 9 gm. of protein per kilogram of body weight per day may be retained (292). This amount, however, does not bring the protein content of the blood of newborn infants to a high level. The protein content of the blood in the newborn period generally has been found to be less than

TABLE 14

RELATION OF BIRTH WEIGHT AND LENGTH TO TOTAL PROTEIN IN MATERNAL DIET DURING LAST SIX MONTHS OF PREGNANCY (100)

Average total protein	Birth weight				Birth length	
	Male infant		Female infant		Male infant	Female infant
gm.	*lb.*	*oz.*	*lb.*	*oz.*	*cm.*	*cm.*
Less than 45	6	8	5	4	47.6	46.8
45–54	7	0	6	14	49.3	48.7
55–64	7	7	7	8	50.2	49.9
65–74	8	0	7	12	51.4	50.3
75–84	8	5	8	1	52.0	51.4
85 and over	9	2	8	8	53.3	52.4

that of adult blood, and in premature infants total serum protein is even lower, usually about 4.5 gm. per 100 ml.

The smaller and younger the infant, the higher is his requirement of protein because of rapid growth. Inefficiency in digesting and absorbing fat (303) makes it necessary to use relatively more protein and carbohydrates for energy. The food recommended for such infants should be high in protein and carbohydrate and low in fat. Gordon and co-workers (301) found that daily weight gains were higher, nitrogen balances were greater, and coefficients of digestibility were not lowered by more liberal protein intakes. They also found that, at equivalent levels of dietary protein, heated human milk and heated cow's milk yielded similar absolute and percentile retentions of nitrogen. Levine (471), from the allowances recommended by the Food and Nutrition Board, estimated the protein demands of infants, including prematures (Table 15).

Colostrum has the high-protein and low-fat proportions ideally suited to the immature digestive system of the newborn infant. If a baby cannot have colostrum, the formula given in the newborn period should simulate it as closely as possible. The fear of giving young infants, particularly immature and small infants, formulas

too concentrated in protein does not have any basis in the physiology of digestion. In European countries, particularly, high-protein feedings have been avoided. When cow's milk is diluted to one-half water, the protein content is about 1.7 per cent and will give a full-term baby 2 gm. or more per kilogram of body weight. For a premature infant, however, this may not be enough, and these infants are benefited by an undiluted skim milk formula with added cane sugar or dextrose.

When the premature infant's need of protein above that contained in breast milk is advanced as a point against the general use of breast milk, it must be remembered that a premature infant is a product of pathologic metabolic processes which require special "treatment" to make up for the lack of storage, for immaturity, and for under-developed functional capacity. These infants require nitrogen to replace and extend their protoplasmic tissue. Premature infants can be fed human milk fortified with dry skim milk, thus maintaining milk secretion by the mother as well as providing ample nourishment for the infant.

TABLE 15
RECOMMENDED DAILY ALLOWANCES FOR PROTEIN, EXPANDED FOR INFANCY (471)

Infant group	Age	Protein in grams			Per cent dietary calories
		Total*	per kg.†	per lb.†	
Premature					
Weight under 2000 gm.	1 week–1 month	3.5	6.4–4.4	2.7–2.0	17
Weight 2000 gm. or more	1 week–1 month	3.5	5.0–4.4	2.3–2.0	15
Premature	1–3 months	3.5	4.4–3.3	2.0–1.5	13
Full term	2 days–3 months	3.5	4.4–3.3	2.0–1.5	13
All infants	4 months–1 year	3.5	4.0–3.0	1.8–1.4	13

* Allowances recommended by Food and Nutrition Board (257).
† Suggested modifications for infants.

Gordon and co-workers (301) and Marples and associates (536) stated that nitrogen retentions averaged 0.3 gm. per kilogram (50 per cent of intake) in premature infants, 0.2 gm. per kilogram (under 40 per cent of intake) in full-term infants under 3 months (537), and 0.15 gm. per kilogram (15 per cent of intake) in infants 5 or more months old (473). Levine (472) reported that in infants protein intakes under 2.2 gm. per kilogram (1 ounce per pound) may lead to negative nitrogen balance. Sixty per cent of the total protein of human milk is present as lactalbumin, which is a complete protein. Milk proteins may be sufficient for the infant until he is 4 months of age, when proteins of animal origin and some vegetable proteins may progressively supplement the milk.

Protein deficiency may result from: low intake, impaired digestion or absorption, loss through urine, vomiting, or fever. Under all circumstances the reserves, whether in muscle or liver, are drawn upon to supply the needs of essential tissue, particularly the blood (70). In spite of the body's physiologic attempts to keep concentration of plasma proteins within the normal range, the osmotic pressure of the tissue fluids imposes a lower limit upon the reserves available. When this limit is reached the

protein level in the plasma falls, reducing colloidal osmotic pressure and permitting fluid to escape from the blood into the extracellular spaces. Dodd and Minot (196) found low values for albumin in most cases of edema in infants, some values being as low as 1.8 gm. per 100 ml. Darrow and Cary (174) found that in premature babies blood protein content usually ranges below the level in full-term infants. In premature infants total blood protein of 5.5 gm. per 100 ml. has been found, of which 3.8 gm. was albumin and 1.7 gm. was globulin, compared with 6.04, 4.41, and 1.6 gm. per 100 ml., respectively, for full-term infants (953). The low plasma protein in premature infants is in accord with their high content of extracellular fluid, which seems to become stabilized in full-term infants by about 6 months but in premature infants may not be accomplished until they are older.

The first signs of protein deficiency (135, 409) are loss of weight, decreased resistance to infection, and poor muscle tone. Clements (135) emphasizes that infants, even with advanced protein deficiency, do not develop the edema typically seen in adults, but become pale and "doughy-looking" owing to water-logging of all tissues. While some believe that premature infants have difficulty in digesting the protein of cow's milk, this is not the experience of Hanna (335), Goldman (292), and Levine and associates (474, 476) who also observed that the metabolism of certain amino acids was completed by increased vitamin C intake. In the nutritional anemias of infancy a contributory role by protein deficit can hardly be neglected, for the protein-globin comprises 95 per cent of the hemoglobin molecule. The extrinsic factor in erythrocyte maturation, according to Bethell and co-workers (55), is of protein nature. These facts are pertinent to the etiology of nutritonal anemias in infancy, beyond the obvious iron or vitamin deficiencies.

Deficiencies of individual amino acids in infants were studied by Albanese and co-workers (10), who found that a tryptophan-deficient diet within 10 days caused an appreciable hypoproteinemia, evidenced largely by decreased albumin level. An isoleucine-poor diet for periods of 2 to 3 weeks did not induce any definite clinical symptoms in the infants. From an experiment consisting of 3 weeks of isoleucine-deficient regimen, infants were estimated to require approximately 90 mg. of L-isoleucine per kilogram per day. Of tryptophan, 30 mg. per kilogram per day was found to be necessary for the maintenance of acceptable weight gains.

COMPOSITION OF MILK

The composition of human colostrum and mature human milk has been determined at various intervals postpartum and in secretion by women of diverse characteristics, from whom samples were obtained by different procedures and analyzed for many components by numerous methods. In a recent publication, Macy and associates (528) compiled data from approximately 250 reports presenting results of analyses of milk selected from over 1500 presentations of values for components of the mammary secretion from "average," "healthy," or "normal" subjects. The summary table (Table 16) shows the composition of human colostrum (1–5 days postpartum), transitional milk (6–10 days postpartum), and mature human, goat, and cow milks. These data provide the best available portrayal of the changes in composition of mothers' milk during lactation and a basis for evaluation of breast feeding versus formulas composed with goat and cow milks.

CALCIFYING PROCESSES

Discussion of possible causes of the occurrence of severe rickets in central Europe during and following the First World War introduced the question of whether rickets was hereditary and detectable at birth. Histological studies of newborn infants' bones were completely negative (741, 973), as were roentgenological examinations (357) and chemical analyses of the blood (355), leading to the conclusion that the prenatal period had little influence on the occurrence of the disease.

As early as 1919, however, Yllpö (999) had found congenital rickets in 5 of 88 cases by roentgenological examination of bones and epiphyseal centers at birth. Later, Maxwell (548, 549) found definite congenital rickets in Chinese infants born to osteomalacic mothers. Wolfe (989) found congenital rickets in three Chinese infants of osteomalacic mothers, two of the infants being stillborn, and histologic studies of their bones and teeth showed fully developed osteoid and dentinoid zones, respectively. Schmorl (741) described histologic rachitic changes in the bones of an infant 6 weeks old and Dunham (207) found clinical rickets in a full-term baby 34 days old. Sontag (803) found well developed rickets in month-old infants of malnourished mothers.

Hess and Weinstock (356) tried to prevent rickets by adding vitamin D to the usual ration for mother rats during gestation, but after weaning a rachitic ration still produced rickets in the young. These authors obtained similar results with human mothers: rickets could not be prevented in infants by giving cod liver oil to the mothers during the last 2 months of pregnancy, even in babies who received only breast milk after birth, but the severity of the rachitic process was influenced by the prenatal dietary supplement. The authors concluded that the problem of rickets must be solved by regulating postnatal feeding.

Other authors (103, 443, 553) demonstrated with animals the great influence of the prenatal period on the development of rickets. They found earlier development of rickets in the young of mothers deficient during gestation than in the young born of mothers having had sufficient vitamin D during gestation. Mellanby (553) showed that with two puppies, born of mothers receiving adequate and vitamin D-deficient diets during gestation and lactation, then given an adequate diet for 4 months followed by a rachitic ration, a disposing factor to rickets was still present in the dog born of the mother with insufficient diet throughout gestation and lactation. When these dogs were $10\frac{1}{2}$ months old, fully developed rickets was present in the dog predisposed to rickets, but the other animal was quite normal. Later, Hess (354) stated: "It has been the experience in the course of an examination of the epiphyses of a large number of newborn infants that peculiar and unexplained epiphyseal margins are evident occasionally—epiphyses instead of being sharp are slightly frayed with a tendency of cupping such as might be determined 'incipient rickets' in later months."

In apparently the first study of metabolism in this century Sillevis (779) found positive phosphorus balances in three primiparas. The French gynecologist Bar (37) reported that he had made similar studies with the same result. In 1910, Hoffström (367) found retentions of calcium, phosphorus, and magnesium by one woman for almost the whole period from the seventeenth week of pregnancy to delivery. The

TABLE 16

SUMMARY VALUES FOR THE PROPERTIES AND THE COMPOSITION OF HUMAN COLOSTRUM, TRANSITIONAL AND MATURE MILK, MATURE GOAT MILK AND MATURE COW MILK (528)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
PHYSICAL PROPERTIES					
ELECTRICAL CONDUCTIVITY					0.0086
GOLD NUMBER	2370	792			
FREEZING POINT °C.					0.546
INDEX OF REFRACTION (at 40°C.)			1.4570		1.4001
OSMOTIC PRESSURE					196
pH VALUE				6.37	6.50
REFRACTIVE CONSTANT					0.2070
SPECIFIC GRAVITY	1.034	1.035	1.031	1.033	1.033
SURFACE TENSION (dynes/sq. cm.)				52.0	52.8
VISCOSITY (at 15°C.)					1.75
FAT CHARACTERISTICS					
FAT MELTING POINT °C.		32*	31		
HEHNER NUMBER				88.2	89.2
HUBL NUMBER					35.2
IODINE NUMBER	(early lactation 60.4)		61.6	28.8	38.4
KIRSCHNER VALUE	(early lactation 0.6)		0.5	17.8	24.0
POLENSKE NUMBER	(early lactation 0.6)		1.2	7.7	1.5
REICHERT-MEISEL NUMBER	(early lactation 1.8)		0.8	27.4	28.8
SAPONIFICATION NUMBER	(early lactation 205.1)		204.7	235.9	248.0
THIOCYANOGEN NUMBER				27	34
SOLUBLE ACIDS				4.5	4.2
CHEMICAL COMPONENTS					
CITRIC ACID mg./100 ml. whole milk				151	217
TITRABLE ACIDITY, % LACTIC ACID				0.199	0.144
INDICAN mcg.†/100 ml. whole milk			30	192	124
WATER, gm./100 ml. whole milk	87	86	88	86	87
ENERGY, CAL./100 ml. whole milk	58	74	71	78	69
TOTAL SOLIDS, gm./100 ml. whole milk	12.8	13.6	12.4	13.6	12.8
ASH, gm./100 ml. whole milk	0.33	0.24	0.21	0.77	0.71
per cent total solids	2.6	1.8	1.7	5.7	5.5
FAT, gm./100 ml. whole milk	2.9	3.6	3.8	4.1	3.8
per cent total solids	22.6	26.5	30.6	30.1	29.7
LACTOSE, gm./100 ml. whole milk	5.3	6.6	7.0	4.7	4.8
per cent total solids	41.4	48.5	56.4	34.6	37.5

* 1–10 days.

† mcg. = micrograms.

TABLE 16—(*Continued*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
CHEMICAL COMPONENTS—Continued					
TOTAL SOLIDS—*Continued*					
PROTEIN, gm./100 ml.					
whole milk	2.7	1.6	1.2	3.4	3.3
per cent total solids	21.1	11.8	9.7	25.0	25.8
ASH, MAJOR COMPONENTS					
CALCIUM, mg./100 ml.					
whole milk	31	34	34	130	126
per cent total ash	9	14	16	17	18
CHLORINE, mg./100 ml.					
whole milk	91	54	43	159	100
per cent total ash	28	22	20	21	14
MAGNESIUM, mg./100 ml.					
whole milk	4	4	4	16	13
per cent total ash	1	2	2	2	2
PHOSPHORUS, mg./100 ml.					
whole milk	14	17	16	106	99
per cent total ash	4	7	8	14	14
POTASSIUM, mg./100 ml.					
whole milk	74	64	55	181	138
per cent total ash	22	27	26	24	19
SODIUM, mg./100 ml. whole milk	48	29	15	41	58
per cent total ash	14	12	7	5	8
SULFUR, mg./100 ml. whole milk	22	20	14	16	30
per cent total ash	7	8	7	2	4
ASH, MINOR COMPONENTS (Milligrams per 100 ml. whole milk)					
ALUMINUM			tr	tr	tr
BARIUM			tr	tr	tr
BORON			tr	0.0177	0.0156
BROMINE			0.912		0.021
CHROMIUM			tr	tr	tr
COBALT					0.00006
COPPER	0.06		0.04	0.04	0.03
FLUORINE					0.016
IODINE	0.012	0.002	0.011*		0.021
IRON	0.12		0.21	0.05	0.13
LEAD			0.016	tr	tr
LITHIUM			tr	tr	tr
MANGANESE	tr		0.0007	0.008	0.002
MOLYBDENUM			tr	0	tr
NICKEL					0.013
RUBIDIUM			1		tr

* Skim milk.

TABLE 16—(*Continued*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
CHEMICAL COMPONENTS—Continued					
ASH; MINOR—*Continued*					
RUTHENIUM					tr
SILICON					tr
SILVER			tr	tr	tr
STRONTIUM			tr	tr	tr
TIN					0
TITANIUM			tr	tr	tr
VANADIUM			tr	tr	tr
ZINC	0.65	1.15	0.66	tr	0.35
SALTS					
(Grams per 100 ml. whole milk)			0.313	0.939	0.901
DI-CALCIUM PHOSPHATE			0.000	0.092	0.175
TRI-CALCIUM PHOSPHATE			0.000	0.062	0.000
MONO-MAGNESIUM PHOSPHATE			0.027	0.000	0.103
DI-MAGNESIUM PHOSPHATE			0.000	0.068	0.000
TRI-MAGNESIUM PHOSPHATE			0.000	0.024	0.000
MONO-POTASSIUM PHOSPHATE			0.069	0.073	0.000
DI-POTASSIUM PHOSPHATE			0.000	0.000	0.230
POTASSIUM CITRATE			0.103	0.250	0.052
SODIUM CITRATE			0.055	0.000	0.222
POTASSIUM CHLORIDE			0.000	0.160	0.000
SODIUM CHLORIDE			0.000	0.095	0.000
CALCIUM CHLORIDE			0.059	0.115	0.119
ANION-CATION RELATIONSHIPS (ACID-BASE EQUIVALENTS) (Milliequivalents per 100 ml. whole milk).					
TOTAL ELECTROPOSITIVE IONS (CATIONS, BASE)	5.85	4.93	4.09	14.22	13.41
CALCIUM	1.54	1.70	1.70	6.49	6.29
per cent total cations	26	34	42	46	47
MAGNESIUM	0.33	0.33	0.33	1.32	1.07
per cent total cations	6	7	8	9	8
POTASSIUM	1.89	1.64	1.41	4.63	3.53
per cent total cations	32	33	34	33	26

TABLE 16—(*Continued*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
CHEMICAL COMPONENTS—Continued					
ANION-CATION RELATIONSHIPS—*Continued*					
SODIUM	2.09	1.26	0.65	1.78	2.52
per cent total cations	36	26	16	12	19
TOTAL ELECTRONEGATIVE IONS (ANIONS, ACID)	4.75	3.76	3.01	11.64	10.44
CHLORINE	2.57	1.52	1.21	4.48	2.82
per cent total anions	54	41	40	38	27
PHOSPHORUS	0.81	0.99	0.93	6.16	5.75
per cent total anions	17	26	31	53	55
SULFUR	1.37	1.25	0.87	1.00	1.87
per cent total anions	29	33	29	9	18
ALKALINE-ASH VALUE (EXCESS OF CATIONS OVER ANIONS)	1.10	1.17	1.08	2.58	2.97
ENERGY DISTRIBUTION (Calories per 100 ml. whole milk)					
ENERGY VALUES REPORTED	58	74	71	78	69
CALCULATED ENERGY					
Fat (gm. × 9.25†)	27	33	35	38	35
Lactose (gm. × 3.95†)	21	26	28	19	19
Protein (gm. × 5.65†)	15	9	7	19	19
TOTAL	63	68	70	76	73
Percentage from FAT	43	49	50	50	48
Percentage from LACTOSE	33	38	40	25	26
Percentage from PROTEIN	24	13	10	25	26
FAT DISTRIBUTION, grams per 100 ml. milk					
FAT, TOTAL	2.9	3.6	3.8	4.1	3.8
LIPOID PHOSPHORUS	0.002	0.003	0.004	0.004	0.004
TOTAL CHOLESTEROL	0.027	0.028	0.020	0.024	0.014
FREE CHOLESTEROL					0.012
LECITHIN			0.078		0.057
SOLUBLE ACIDS				4.5	4.2
FATTY ACID DISTRIBUTION (Grams per 100 gms milk fat)					
Saturated Fatty Acids					
BUTYRIC ACID	0.2		0.4	2.6	3.1

† Atwater factors for heat of combustion of fat and protein in "dairy products" and for "sugar" taken from Maynard, L. A., The Atwater System of Calculating the Calorie Value of Diets, J. Nutrition *28*: 443–452, 1944. For "available" energy or "physiological fuel values," the factors 8.80 for fat, 3.85 for lactose, and 4.25 for protein should be substituted for the heat of combustion values and the energy distribution recalculated accordingly.

TABLE 16—(*Continued*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
CHEMICAL COMPONENTS—Continued					
FATTY ACID DISTRIBUTION—*Continued*					
CAPROIC ACID	0.1		0.1	2.3	1.0
CAPRYLIC ACID	0.4		0.3	2.7	1.2
CAPRIC ACID	2.2	1.8‡	1.7	8.4	2.6
LAURIC ACID	1.8	5.6‡	5.8	4.5	2.2
MYRISTIC ACID	3.8	9.4‡	8.6	11.1	10.5
PALMITIC ACID	26.2	23.6‡	22.6	28.9	26.3
STEARIC ACID	8.8	7.8‡	7.7	7.8	13.2
as ARACHIDIC ACID	3.8	1.4‡	1.0	0.4	1.2
Unsaturated Fatty Acids					
DECENOIC ACID	0.2	tr‡	0.1	0.2	0.2
DODECENOIC ACID	0.1	0.1‡	0.1	0.3	0.2
TETRADECENOIC ACID	0.2	0.8‡	0.6	0.5	1.1
HEXADECENOIC ACID	2.4	3.2‡	2.9	2.5	3.1
OLEIC ACID	36.6	34.6‡	36.4	27.0	32.2
OCTADECADIENOIC ACID	6.8	7.1‡	8.3	2.6	1.6
OCTADECATRIENOIC ACID	0.3		0.4		
as EICOSADIENOIC ACID	4.6		2.4		
C 20–22 ACID	10.2	4.6‡	4.2	0.4	1.0
OCTADECATETRENOIC ACID			0.2		
ARACHIDONIC ACID	1.7		0.8	1.5	1.0
PHOSPHORUS DISTRIBUTION mg./100 ml. whole milk					
PHOSPHORUS, ACID SOLUBLE, TOTAL				86	82
PHOSPHORUS, ACID SOLUBLE, INORGANIC					68
PHOSPHORUS, ACID SOLUBLE, ESTER Organically bound					10.2
PHOSPHORUS, ACID INSOLUBLE, TOTAL					26.0
PHOSPHORUS, RIBONUCLEIC ACID			0.2	2.3	1.6
PHOSPHORUS, INORGANIC, TOTAL			5.3	79	80
PHOSPHORUS, ORGANIC, TOTAL				14.4	

‡ 1st 3 weeks.

TABLE 16—(*Continued*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
CHEMICAL COMPONENTS—Continued					
NITROGEN DISTRIBUTION (Grams per 100 ml. whole milk)					
TOTAL NITROGEN	0.515	0.317	0.227	0.574	0.551
PROTEIN NITROGEN	0.424	0.251	0.188	0.534	0.518
per cent total nitrogen	82	79	83	93	94
NON-PROTEIN NITROGEN	0.091	0.066	0.039	0.040	0.033
per cent total nitrogen	18	21	17	7	6
PROTEIN DISTRIBUTION (Grams per 100 ml. whole milk)					
CASEIN	1.2	0.7	0.4	2.5	2.8
per cent total protein	44	44	33	74	85
LACTALBUMIN		0.8	0.3	0.4	0.4
per cent total protein		50	25	12	12
LACTOGLOBULIN		0.5	0.2	0.3	0.2
per cent total protein		31	17	9	6
WHEY PROTEIN	1.7		0.6	1.1	0.6
per cent total protein	63		50	32	18
PROTEIN NITROGEN DISTRIBUTION (Milligrams per 100 ml. whole milk)					
CASEIN NITROGEN	188	110	63	392	440
per cent total protein nitrogen	44	44	34	73	85
LACTALBUMIN NITROGEN		126	47	63	63
per cent total protein nitrogen		50	25	12	12
LACTOGLOBULIN NITROGEN		78	31	47	31
per cent total protein nitrogen		31	16	9	6
WHEY NITROGEN	267		94	173	94
per cent total protein nitrogen	63		50	32	18
NON-PROTEIN NITROGEN COMPONENTS (Milligrams per 100 ml. whole milk)					
CREATINE			3.3		2.4
CREATININE			2.2		1.0
UREA		23.3	32.2		19.5
URIC ACID			4.6		1.5

TABLE 16—(*Continued*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
CHEMICAL COMPONENTS—Continued					
NON-PROTEIN NITROGEN DISTRIBUTION (Milligrams per 100 ml. whole milk)					
AMINO ACID NITROGEN.		4	6		4
per cent non-protein nitrogen		6.1	15.4		12.1
CREATINE NITROGEN (Factor = 3.1)			1.1		0.8
per cent non-protein nitrogen			2.8		2.4
CREATININE NITROGEN (Factor = 2.7)			0.8		0.4
per cent non-protein nitrogen			2.0		1.2
UREA NITROGEN (Factor = 2.1)		11.1	15.3		9.3
per cent non-protein nitrogen		16.8	39.2		28.2
URIC ACID NITROGEN (Factor = 3.0)			1.5		0.5
per cent non-protein nitrogen			3.8		1.5
TOTAL AMINO ACID DISTRIBUTION (Milligrams per 100 ml. whole milk)					
Dispensable Amino Acids					
ALANINE			35		75
per cent total protein			2.9		2.3
per cent from casein			22.8		85.3
ASPARTIC ACID			116		166
per cent total protein			9.7		5.0
per cent from casein			15.5		97.6
CYSTINE		48*	29		28
per cent total protein			2.4		0.8
per cent from casein			6.9		35.7
GLUTAMIC ACID			230		680
per cent total protein			19.2		20.6
per cent from casein			36.5		89.4
GLYCINE			0		11
per cent total protein			0.0		0.3
per cent from casein					100
PROLINE			80		250
per cent total protein			6.7		7.6
per cent from casein			45.0		109.6

* 2–9 days.

TABLE 16—(*Continued*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
CHEMICAL COMPONENTS—Continued					
TOTAL AMINO ACID DISTRIBUTION—*Continued*					
SERINE			69		160
per cent total protein			5.7		4.8
per cent from casein			31.9		94.4
TYROSINE		105*	61		191
per cent total protein			5.1		5.8
per cent from casein			37.7		87.4
Indispensable Amino Acids					
ARGININE	74	135	50		122
per cent total protein	2.7	8.4	4.2		3.7
per cent from casein			28.0		86.9
HISTIDINE	41	44	23		72
per cent total protein	1.5	2.8	1.9		2.2
per cent from casein			30.4		87.5
ISOLEUCINE	101	101	80		221
per cent total protein	3.7	6.3	6.7		6.7
per cent from casein			31.2		77.4
LEUCINE	166	152	154		398
per cent total protein	6.1	9.5	12.8		12.1
per cent from casein			31.8		75.9
LYSINE	118	118	75		243
per cent total protein	4.4	7.4	6.2		7.4
per cent from casein			29.3		78.2
METHIONINE	25	30	22		93
per cent total protein	0.9	1.9	1.8		2.8
per cent from casein			45.4		87.1
PHENYLALANINE	70	88	64		181
per cent total protein	2.6	5.5	5.3		5.5
per cent from casein			35.9		85.1
THREONINE	85	88	59		152
per cent total protein	3.1	5.5	4.9		4.6
per cent from casein			30.5		80.3
TRYPTOPHAN	32	34	22		46
per cent total protein	1.2	2.1	1.8		1.4
per cent from casein			27.3		73.9
VALINE	117	120	87		233
per cent total protein	4.3	7.5	7.2		7.1
per cent from casein			23.0		79.4
VITAMINS					
(Values per 100 ml. whole milk)					
Fat-Soluble Vitamins					
VITAMIN A, mcg.	89	88	54		37
CAROTENOIDS, mcg.	112	38	32		39
VITAMIN D, U.S.P. UNITS			0.42		
VITAMIN E, mg.	1.28	1.32	0.66		0.06
VITAMIN K, Dam-Glavind Units			26		100

*2–9 days.

TABLE 16—(*Concluded*)

	1–5 days	6–10 days	Mature milk		
			Human	Goat	Cow
VITAMINS—(*Continued*)					
Water-Soluble Vitamins					
ASCORBIC ACID, mg.	4.4	5.4	4.4	1.3	1.8
BIOTIN, TOTAL, mcg.	0.1	0.4	0.4	6.3	3.5
CHOLINE, mg.			9		13
CHOLINE, FREE, mg.			2		4
FOLIC ACID, mmg.			0.22	<3	0.29
INOSITOL, TOTAL, mg.			39	21	13
INOSITOL, FREE, mg.			44		6
NICOTINIC ACID, mcg.	75	175	172	273	85
PANTOTHENIC ACID, mcg.	183	288	203	289	350
PYRIDOXINE, mcg.			11	7	48
RIBOFLAVIN, TOTAL, mmg.	31.1	36.9	46.9	114	158
RIBOFLAVIN, FREE, mcg.	19.0	24.0	24.2		
THIAMINE, TOTAL, mcg.	19	6	15	48	42
THIAMINE, FREE, mcg.	0.4	0.8	4.8	8.6	23

daily calcium intake ranged from 1.2 to 2.4 gm., the phosphorus intake from 1.7 to 2.4 gm., and Hoffström showed that the maternal body acquired mineral reserves beyond the needs for development of the fetus, preparation for the puerperium, and lactation. Landsberg (456) found positive balances for 14 women receiving daily calcium intakes of 1.8 to 2.9 gm. and phosphorus intakes of 2.1 to 3.1 gm.

Whether the mother organism gives up her own reserves to the young when deficiency is present during gestation has been of great interest. In 1923, female rats given a low calcium diet by Toverud (880) showed low calcium retentions, increased magnesium retentions, and reductions in blood calcium from 11–12 mg. to 5 mg. per 100 ml. of serum. The bones were reduced in total ash, calcium, and phosphorus, with a possible increase in magnesium content. In 1925, Sherman and MacLeod (765) reported that the bodies of rats that had borne and suckled young contained less calcium and phosphorus than those of rats that had not reared young. If the diet was adequate and the intervals between pregnancies not too short, equilibrium was established at these low levels of calcium and phosphorus reserves. Losses in rearing each litter were regained in the intervals if the calcium and phosphorus intakes were increased 10 to 20 per cent in pregnancy (304).

To determine whether varying disposition to rickets and dental caries might be explained by dietary deficiency during the prenatal period, the Toveruds studied the metabolism of 100 pregnant women in Oslo (883). The average daily intakes of calcium seldom exceeded 1 gm., which Sherman and Lanford (764) determined to be the requirement for normal adults without extra biological demands. Studies of 27 women living in a home for expectant mothers during the last 2 to 3 months of pregnancy showed 21 to be in negative calcium balance and 12 to be in negative

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phosphorus balance. Retentions were obtained, or losses reduced, by increasing the daily calcium intakes to 1.6–2 gm. and the phosphorus intakes to 1.8–2 gm. In some, addition of cod liver oil to the usual diet without increasing the calcium intake produced positive balances. In the majority, however, cod liver oil or a vitamin D preparation (vigantol) did not affect a negative balance when the calcium and phosphorus intakes were low. One year after the preliminary report of these studies several papers (142, 388, 524) showed that in America also the calcium intake of pregnant women was often below 1 gm. daily and that negative calcium balances were common with this intake level and might occur even with intakes above 1.5 gm. per day when biological demands prior to the experimental period had been great.

The actual calcium and phosphorus needs during pregnancy are contingent upon nutritional state, which has been determined by previous nutritional and biological demands, infections, and other depleting diseases. That physiologic constitution of the woman plays a great role was shown plainly by Hummel and co-workers (387). An 18-year-old primipara with an unsatisfactory nutritional background showed a calcium retention of 46.3 gm. during the final 65 days of gestation, whereas for a woman with a satisfactory nutritional history the value was only 24.7 gm. during the same length of time and under comparable conditions. The question was whether the negative balance often found in pregnancy was harmful to the mother or the fetus. The women themselves did not present symptoms of this negative calcium balance which might represent a daily loss of 0.5 gm.

The impossibility of following exactly the effects of negative calcium balance upon the human mother, fetus, and infant led the Toveruds (884) to reproduce in dogs the negative calcium and phosphorus balances found in women. When bitches were given a diet low in calcium, phosphorus, and fat-soluble vitamins they suffered a great loss of calcium during gestation. One dog lost about 10 per cent of its original calcium content and during lactation additional loss was shown by low values for blood serum calcium and phosphorus. Chemical analyses of the bones of the mother and the young revealed that losses of calcium and phosphorus from the mother were marked, but histological and roentgenological examinations were negative. Furthermore, when the young were given a deficient diet after weaning they quickly developed signs of rickets with marked deformities of the extremities. Rickets was more pronounced and appeared earlier than in puppies born and nursed by a mother given the experimental diet from the day of delivery. These last puppies again showed a more marked rickets than puppies born and nursed by a mother on a normal ration but given the experimental diet after weaning. Chemical analysis, microscopic sections, and X-ray pictures, all showed changes corresponding to the duration of the preceding nutritional deficiency. The metabolic processes during gestation and lactation had disposed the young to early development of rachitic processes when the deficiency continued postnatally. When cod liver oil was added to the deficient diet, osteoporosis instead of rickets occurred in puppies under otherwise identical experimental conditions.

Only by chemical analysis of the bones of newborn puppies was it possible to detect the pathological changes resulting from the deficient diet during fetal life. Toverud

(889) found this to be true in newborn infants also. In infants born of mothers whose diets had been poor in calcium, the calcium and phosphorus contents of the bones were lower than in those of infants born of mothers whose diets had been adequate in calcium, and histological changes with enlarged osteoid zones were noticed in some of the infants. Distinct differences in calcification of the teeth (888) also were noticed in newborn infants of mothers who had received poor diets during pregnancy. Other changes were noted in the teeth and jaws of the infants, such as edema and hemorrhage in the enamel organ, which explain hypoplasia often found in the deciduous teeth. From the findings, it seems evident that many infants are born with low stores of calcium, phosphorus, and vitamin D.

Clinical methods used with newborn infants rarely give information about possible changes as a result of deficiencies in fetal life. Coons and Blunt (142) observed that epiphyses of 8-day-old infants born of mothers with poor retentions of calcium and phosphorus during pregnancy were fringy and poorly calcified. Sontag (803) found by X-ray studies of a group of newborn infants that the severity of round bone scars resulting from the birth process is much greater in those children born of mothers whose diet was greatly defective, confirming his earlier findings (804, 805).

The postnatal feeding of the infant, then, determines whether the stores of the various calcifying factors will be augmented to meet the daily demands of the infant for normal growth and development. Under ordinary conditions pregnant women do not evidence symptoms of minor deficiencies of calcium and phosphorus. The losses from the mother organism take place, according to Bauer and associates (44), in the trabeculae of the spongiosal substance. Such a loss rarely elicits symptoms unless marked, when an osteomalacia may result. In the publications of Maxwell (549) and Wolfe (989), describing Chinese cases of congenital rickets, the mothers had had tetany and at the time of the study had osteomalacia.

In general, because of the demands of growth in both the maternal and fetal bodies, the requirements for calcium and phosphorus during pregnancy, particularly during the 2 last months, should be considered to be 1.6 to 2 gm. of calcium and 1.8 to 2 gm. of phosphorus, with added vitamin D. In practice this means that 1 liter or quart of milk, fruit, and vegetables, and 400 I.U. of vitamin D per day should be included in every pregnant woman's diet. Of the infants of 1531 Norwegian women who received such a diet, less than 1 per cent showed even slight calcification defects such as early craniotabes and bowing of the legs. Women supervised during the war years were not getting more than 0.75 liter of milk daily, but with the addition of cod liver oil to the diet and 0.4 per cent calcium carbonate to the bread, the requirement for calcium was evidently met, for the general health of the mothers and infants was very good.

In China, Liu and co-workers (484) found that with an adequate supply of vitamin D the same degree of calcium retention was maintained on a somewhat lower intake of calcium, but that with severe vitamin D depletion a high level of calcium would not maintain the individual in balance. They concluded that vitamin D is a more important factor than the actual level of calcium intake in determining the extent of retention, provided a reasonable amount of calcium is present in the diet. A greater mineral conservation seemed to be present in these Chinese women than in other

pregnant women. These authors also decided that when dietary habits accustom a subject to a lower intake she adjusts to this lower level and the requirement for reproductive activity is correspondingly reduced. They call attention to the fact emphasized by Macy and her group: that the calcium requirement of a pregnant woman is not a fixed one but may be conditioned by such factors as previous skeletal store, dietary custom, and state of vitamin D nutrition.

Burke and associates (101) found the calcium content of the diets of 17 per cent of 216 pregnant women was below 0.75 gm. daily and of 23 per cent, below 1.0 gm. All stillborn infants, all infants who died within a few days of birth except one, most infants who had marked congenital defects, all premature and all functionally immature infants were born to mothers whose diets during pregnancy were very inadequate (101).

Obermer (639, 640) from results of balance studies in England during the war concluded that the average calcium intake of pregnant women not receiving supplements of a calcium salt was insufficient to insure positive balances. His data indicated that an intake of not less than 2 gm. of calcium per day from the beginning of pregnancy to the end of the seventh month, and 2.5 gm. from the eighth month to term should be considered minimum safety levels, accompanied by supplements of vitamin D. Of 227 women examined at different intervals in pregnancy (642), 80 per cent of those not receiving calcium or calciferol supplements showed negative calcium balances. The explanation of negative balances found in women given both adequate supplements of calcium phosphate and high doses of calciferol probably lies in the autonomic imbalance which resulted from the pressures of war. However, persons with low intakes for years may not show good retentions of calcium until several months after a good dietary regimen has been established, which may, in part, explain Obermer's findings of constant negative balances even with high intakes.

The influence of dietary calcium on the development and resistance of teeth has been discussed widely. In most of the experimental work, however, both calcium and vitamin D deficiencies have been present, producing deficient fetal calcification of both bones and teeth, with development of enlarged dentinoid zones. The result of calcium deficiency only is osteoporosis of bones. The question of dental caries in relation to prenatal feeding is complicated, since in recent years postnatal feeding and geographic dietary factors have been shown to play dominant roles in dental caries. Burke (98) believes she found a significant relationship between the calcium intake of mothers during the latter part of pregnancy and the incidence of caries in the deciduous teeth of 123 children. Berk (52) found in a recent study of 198 5-year-old children having 5 or fewer teeth affected with caries and those with 15 or more teeth affected that the chief factor was the mother's milk intake during gestation.

Massler and co-workers (545) observed the calcification of teeth prior to birth to be fairly homogeneous and dense, while from the end of the neonatal period to 10 months of age it was not homogeneous and was easily affected by subclinical disturbances. They stated that the enamel and dentin formed during the first 3 months of life showed relatively better calcification than that formed during the subsequent 6 months, and they believed that fetal mineral reserves were not exhausted in the earlier months. Greater resistance to dental caries was found in Norwegian children

whose mothers' diets and general health were supervised during pregnancy and postpartum (903). The question of the influence of micro- and macroscopic hypoplasia of the enamel in the development of dental caries (559, 563, 564, 565, 566) is unsettled. Possible remineralization in postnatal life giving rise to an increased density and therefore greater resistance to external destructive factors must be considered. The years of war, particularly in the northern European countries, showed conclusively that, in addition to the general factors influencing calcification of the teeth, local dietary factors after the eruption of teeth have a deciding influence on the production of dental caries.

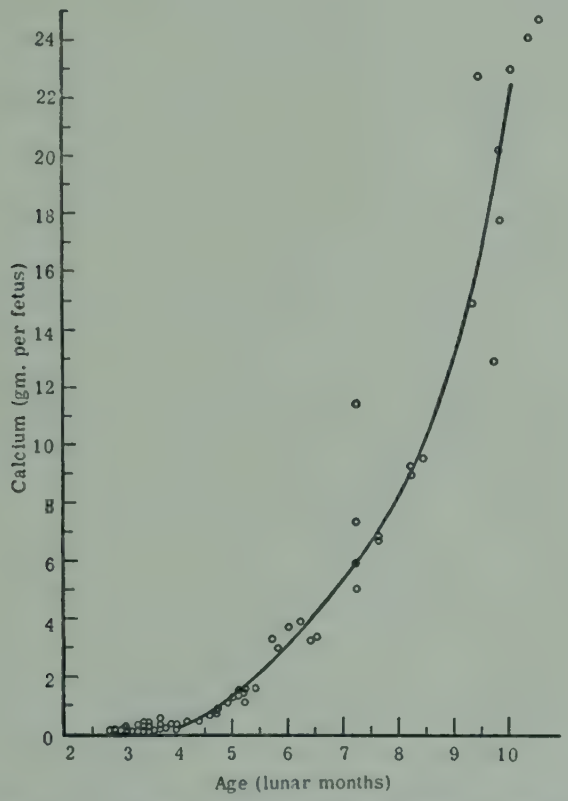

FIG. 4. CALCIUM CONTENT OF THE HUMAN FETUS

Published analyses of human fetuses (285, 525) have shown the accumulation of calcium in the fetus and its adnexa. From the third to the seventh month the gain was about 50 mg. per day, increasing to about 120 mg. until the tenth lunar month, when there was a sharp rise to about 450 mg. Michel (579) found a daily fetal accumulation of 456 mg. of calcium, which is 50 per cent of the adult calcium requirement of 1.0 gm. Obermer (642), on the basis of Mitchell and Curzon's figures, stated that the fetal retentions of calcium during the last 7 lunar months of pregnancy were 25, 50, 84, 175, 234, and 300 mg., respectively. A recent publication (415) assembled data from the literature which could be compared on the basis of fetal age as calculated from body length, and from analyses for calcium in 92 human fetuses a curve (Figure 4) was fitted showing the increment during gestation.

Stearns (814) reported that 98 per cent of body calcium is found in bone. The rest

is contained in the blood and body cells. The relative, as well as the absolute, body content of calcium increases steadily throughout the fetal period, so that at birth the body of a normal infant weighing 3000 gm. contains about 25 gm. of calcium. While the percentage of calcium in the fetal body increases constantly, the percentage of body weight consisting of calcium becomes smaller after birth, the amount depending upon the postnatal feeding of the infant.

Calcium is excreted through the bowel, the unabsorbed and the excreted calcium amounting usually to between 100 and 150 mg. The loss through the kidney is insignificant. The low retention of calcium directly after birth does not seem to be the result of lowered absorption, because increasing the amounts of calcium in food intake leads to a larger fecal loss but at the same time an increased retention takes place. The retention seems to depend primarily on the amount of calcium in the food offered the infant; thus, low retention in the neonatal period may be primarily the result of a low calcium intake and may be the explanation of the so-called "birth lines" or "neonatal lines" seen with moderate frequency in the teeth formed during this period.

Calcium in the blood of newborn infants (874) averages 9.33 mg. per 100 ml., ranging from 7.7 to 11.1 mg., and in cord blood (188) averages 11.53 mg., ranging from 9.0 to 13.1 mg. The premature infant has a lower percentage of calcium at birth compared with the full-term infant. The Bakwins (31) found the concentration of calcium in the serum of both premature and full-term infants to be about 1 mg. per 100 ml. above that in the mother's blood, increasing during the first 3 days of life. Diffusible serum calcium has been found in cord blood averaging 5.3 mg. per 100 ml. of filtrate (16,700) up to the age of 3 weeks.

Phosphorus is contained in the skeleton in a ratio to calcium ranging from 2.21:1 to 2.23:1 (814). The ratio of nitrogen to phosphorus varies with different tissues, being about 15:1 for muscle and 13:1 for liver. For the body as a whole the ratio of 17:1 is used. Full-term infants with a birth weight of 3000 gm. contain about 14.5 gm. of phosphorus and 60 gm. of nitrogen. According to the calcium/phosphorus ratio, about 11.2 gm. of phosphorus would be contained in the skeleton and only about 3.2 gm. in the soft tissue, making the ratio of nitrogen to phosphorus 18.8 for the newborn infant. The newborn infant has a low muscle content of phosphorus compared to that of the adult, altering the nitrogen/phosphorus ratio.

The newborn infant seems (814) to be able to absorb and retain a considerably higher amount of phosphorus than is contained in human milk. With artificial feeding the kidney becomes the chief organ of excretion and 60 to 70 per cent of the phosphorus excretion is in the urine.

Inorganic phosphorus is greater in the blood serum of the newborn infant than in that of the mother. Values for newborn infants vary from 3.5 to 5.4 mg. per 100 ml., the larger value being observed in blood from infants whose mothers had had good diets during pregnancy (814). In later infancy, values from 5 to 7 mg. per 100 ml. have been found accompanying good dietary intakes of vitamin D.

The question is whether the calcium and phosphorus content of an infant at birth always is the same or varies according to the prenatal health and nutritional condition of the mother. Without clinical signs of disturbed calcium metabolism at birth, the calcium and phosphorus contents of the skeleton of newborn infants may be low

owing to maternal deficiencies of calcium, phosphorus, and vitamin A during pregnancy (889). With insufficient vitamin D also, rickets might be present (548, 989, 999). These conditions in the prenatal period also may predispose the infant to early occurrence or later development of rickets (741, 883), depending upon the postnatal feeding of the infant. Figure 5 shows the accretion of phosphorus in the fetus during gestation as indicated by the results of analyses of 92 fetuses (415).

The rapid growth of early infancy is a difficult period for the infant; he is becoming adjusted to the new, extrauterine environment in which he must digest and absorb his own food. His capacity is small, his need large. Salts of both calcium and phosphorus have relatively low solubilities at the pH of intestinal contents and are absorbed with considerable difficulty. The ingestion of vitamin D, or its production within the body through action of ultra-violet irradiation, increases the amount of absorption of both of these substances from the gastrointestinal tract.

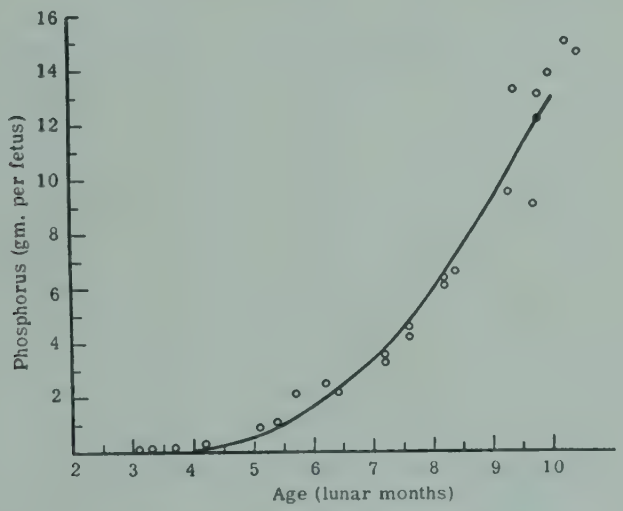

FIG. 5. PHOSPHORUS CONTENT OF THE HUMAN FETUS

Stearns (815) showed in 1939 that neither the breast-fed nor the artificially fed infant retains sufficient calcium and phosphorus to maintain the bone mineral content at its birth percentage, even when vitamin D is given from the first week. The low calcium retention after birth results in a depletion of this mineral in all infants. Many pediatricians interpret the fact that the long bones of the well developed fetus at term are almost completely filled with cancellous bone as evidence that the bone mineral at birth is in part storage mineral for use during these first months of rapid growth. Whether depletion of the skeleton directly after birth produces pathological conditions in infants depends on the prenatal and postnatal nutrition and length of the gestation period. An infant born at term following adequate prenatal nutrition will have a storage of bone mineral sufficient to prevent development of rickets if he is well nourished postnatally.

The values reported for calcium in breast milk range from 150 to 610 mg. per liter with an average value of 340 mg. (Table 16). Calcium retention from breast milk in early infancy has been found to average 48 mg. daily, increasing to the age of

about 8 months, when retentions average 200 mg. of calcium per day (815). With an average daily weight gain of 25 gm. during the first 3 months of life, 20 gm. in the second 3 months, and about 16 gm. in the next 6 months, the percentage of calcium in the body at birth probably is not again achieved by breast-fed infants before the last 3 months of the first year of life.

Drummond and co-workers (203) found in human milk 250 to 410 mg. of calcium and 100 to 180 mg. of phosphorus per liter, and mothers ingesting diets low in calcium produced milk of low calcium content, 177 mg. to 299 mg. per liter. Garry and Wood (279) believed that during lactation women were less able to absorb calcium than during pregnancy, and that during lactation the majority of women are in negative calcium balance. Anderson and Brown (17) reported a case of lactational osteomalacia and tetany with a serum calcium of 7 mg. per 100 ml. The mother's diet had been low in calcium and a very satisfactory response was obtained to an increased calcium intake.

The important question is whether breast milk low in calcium indicates need for supplements of specific calcium salts and vitamin D. In Norway (884) it was possible to eliminate negative calcium balances during lactation by adding calcium and vitamin D to the mothers' diet, and the calcium content of the mothers' milk increased from 213 to 412 mg. per 100 ml. Liu and associates (483) found that addition of vitamin D alone changed calcium balance from negative to positive but addition of calcium to the diet was necessary to increase the calcium content of the milk. The addition of pure food factors always must be evaluated in relation to other factors in the feeding. Calcium given in excess must be excreted combined with phosphorus. If a diet is low in phosphorus, a requirement for extra amounts to excrete with calcium is fulfilled by withdrawal from the body supply. Supplementation with various single nutritional factors to counteract deficiencies is questionable, in view of our knowledge that the proper balance between the various food factors is of the utmost importance. Natural foods are preferable sources for maintenance of the normal calcium content of breast milk. Duckworth and Warnock (206) advocate natural food as the proper means of supplementing diets when deficiency is present, as do Dieckmann and co-workers (193).

The infant born 6 weeks or more prematurely has no store of bone mineral upon which to draw; his gastric capacity is so small that if he is fed only human milk, the amounts of calcium and phosphorus ingested do not provide sufficient mineral for the rapid growth of bone, even though all ingested could be retained (814). Prematurely born infants fed human milk, therefore, show still more drastic reductions in body percentages of calcium after birth, which explains their great liability to rickets. In artificial feeding the calcium retention depends on the composition of the milk mixture. When diluted cow's milk is fed without vitamin D the retention of calcium is poor, with a decrease in the relative calcium content of the body even more rapid than in breast-fed infants without vitamin D addition. When, however, undiluted cow's milk is given with 300 to 400 I.U. of vitamin D, about 3 times as much calcium is provided and about 100 mg. per day are retained during the first month of life, 300 to 400 mg. at the age of 4 to 10 months. Thus, the infant early seems to be able to absorb and retain calcium in far greater amounts than would be expected from the calcium content of human milk.

The excretion of calcium both in the intestine and in the urine (435) is dependent on the dietary calcium. Infants fed cow's milk or calcium salts of equal alkalinity excrete larger amounts of calcium in the urine than wholly breast-fed infants. The normal daily urinary excretion has been found to be 20 mg. (814).

There has been much discussion as to the desirability of high calcium retentions in infancy and the possibility of supermineralization being harmful, but infants receiving high intakes of calcium, such as undiluted cow's milk, seem to develop very well when 300 to 400 I.U. of vitamin D per day is given simultaneously.

Some investigators have regarded the depletion of calcium following birth as "physiological," a means to use the excess store present at birth. The rather common occurrence of rickets in breast-fed infants not taking vitamin D seems to disprove this contention and indicates that depletion after birth is the result of utilization under conditions of inadequate intake. Artificially fed infants are more susceptible to infection, especially upper respiratory infections, than are breast-fed infants. During these infections the retentions of calcium and phosphorus drop to zero, or both may be lost from the body in surprisingly large amounts. It seems desirable, therefore, that artificially fed infants maintain higher stores of bone minerals, especially premature and twin infants with low calcium contents at birth. Jeans and Marriott (409) advocate fortifying human milk with skim milk supplemented with an ample amount of vitamin D for premature infants.

VITAMIN D

The D vitamins comprise a number of isomeric sterol derivatives which are found chiefly in the livers and viscera of fish and the livers of animals fed on fish and in the yolks of eggs. The two most important in nutrition are vitamin D_2 (activated ergosterol, calciferol) and vitamin D_3 (activated 7-dehydrocholesterol) which are found in fish liver oils. They are produced in animals by irradiation of precursors, called provitamins, which occur in the plant kingdom. The activation encompasses a series of reactions rather than one, and over-activation transforms the provitamin into non-calcifying compounds which may be highly toxic. The human body is able to synthesize provitamin D_3 (7-dehydrocholesterol), which is activated in the skin and returned to the blood for storage in the liver or use by the body. Ultra-violet rays from the sun or from artificial sources also act on cholesterol in the skin, forming vitamin D (409). Outside the equatorial zone the greatest part of the body surface is covered with clothing which prevents much of this transformation.

The action of vitamin D is to increase the "net absorption" of the calcium and phosphorus of food. It seems to increase the permeability of the intestinal mucosa to calcium salts without changing the permeability of other membranes, leading to increased serum calcium and decreased activity of the parathyroid glands, thereby decreasing the rate of phosphate excretion by the kidney. Vitamin D appears also to exert some direct effect on the calcification of growing bones, because when large amounts of calcium and phosphate are injected into rachitic animals, bone of normal density is formed but its histological structure is abnormal. According to Shohl (768) there is no reason to believe the cells and matrices concerned in bone growth and maintenance are defective in the absence of vitamin D or are directly acted upon by vitamin D. Investigators agree that in the absence of vitamin D a decrease of calcium

or phosphate ions in the blood retards or prevents calcification of cartilage. This decreased precipitating level results from inefficient absorption of calcium from the intestinal tract. The principal action of vitamin D, then, is to reestablish efficient calcium and phosphorus absorption by restoring the concentration of the ions in the blood plasma so that calcification can take place.

The vitamin D content of breast milk seems to be little influenced by the maternal diet. Drummond and co-workers (203) found 4 I.U. of vitamin D per 100 ml. of breast milk from women receiving less than 100 I.U. per day. Seven women with daily intakes over 100 I.U. secreted in their milk about 8 I.U. per 100 ml., which could not be increased by giving the mothers larger amounts of vitamin D. Polskin and associates (670) gave mothers very large intakes of vitamin D, but not more than one per cent of the administered vitamin was recovered in the milk. Harris and Bunker (339) found only 0.3 I.U. vitamin D per 100 ml. of milk. It is evident that even with an intake of 1000 ml. of milk per day an infant cannot receive more than 80 I.U. of vitamin D per day from his mother's milk, and rickets may occur even if calcium is better absorbed from breast milk. From the literature it appears that marked rickets may occur in breast-fed infants. Even if vitamin D does not easily pass over in breast milk, a mother should receive the recommended daily intake of 400 I.U. of vitamin D during lactation.

While the postnatal form of vitamin D deficiency, rickets, has been studied intensively, the prenatal effects of vitamin D deficiency are still obscure. Discussion of whether congenital rickets exists has persisted for years. The findings of Yllpö (999), Maxwell (548, 549), and Wolfe (989) establishing the occurrence of disturbances in the calcification process during fetal life have been confirmed by roentgenological examinations and by chemical and histological studies of bones and teeth of newborn infants (888, 889).

In 1938 Sontag and Harris (805) found a close relationship of the torsal striae noticed in roentgenograms taken at the age of 1 month to the diet and condition of the mothers during pregnancy. The incidence of persistent nausea and vomiting was much greater in mothers of infants with striae. In infants of mothers in poor health and of unusually low economic status, striae developed. Todd and co-workers (874) found a definite seasonal variation in the blood calcium levels of newborn infants, with higher figures in autumn and winter. All infants born of mothers with three or more children showed significantly lower calcium levels than first-born infants. The calcium-phosphorus ratio followed the seasonal variation in serum calcium. A drop in blood calcium was found during the first 4 days of life by Denzer and associates (188).

There is, then, definite proof that calcification may be disturbed in fetal life, probably as a result of vitamin D deficiency superimposed on low calcium and phosphorus utilization during the prenatal period. Experimentally, this congenital change in calcium metabolism has been shown to have a distinct bearing on the development of rickets postnatally, pointing to a lack of storage of the fat-soluble vitamin. Very few studies have been made of the congenital store of vitamin D, but in 1935 Toverud and Ender (890) determined the vitamin D contents of the livers of 44 stillborn infants and in 24 found none of the vitamin, in 15 only small amounts, and in 5 enough vitamin D to produce complete healing of rickets in rats. The mothers of the

5 infants had had very good diets during pregnancy: 4 had had eggs regularly, the fifth had had cod liver oil daily, and all had received 1.5 liters of milk per day.

From these results it seems necessary to consider all newborn infants of mothers whose diets have included little vitamin D as lacking adequate storage of vitamin D. With a superior postnatal diet, symptoms of deficiency may be avoided and the infant's storage rapidly reestablished, but with insufficient postnatal intake or poor absorption or utilization, rickets will result. On the other hand, good prenatal storage will offset a deficient diet postnatally or counteract possible deficiency from an intercurrent infection or other disease.

Vitamin D deficiency with clinical symptoms is rare during pregnancy, at least in Europe and the United States. In China and India, however, it is relatively frequent, even in recent years, although the small stature and fine bone structure of people in those countries is supposedly the result of adaptation to diets low in protein and calcium. Day (184) reported that as late as 1944 50 per cent of all pregnant Indian women showed marked symptoms of osteomalacia, often so marked that the mothers were practically invalid. One-third of all infants and children were rachitic in the Punjab district of northern India where the diets included little other than coarse cereals. Green-Armytage (310, 311) also has described the difficulties osteomalacia produces in India.

Liu and co-workers (484) found that Chinese women seemed to require less calcium than European and American mothers for maintenance and that osteomalacia was cured quickly during pregnancy by provision of proper amounts of calcium, phosphorus, and vitamin D. Even when vitamin D was limited, the calcium requirement during pregnancy seemed to be even lower than 1 to 1.3 gm. The authors emphasize that previous dietary habits greatly influence the requirement for calcium, and they consider the high phosphorus content of the Chinese diet the main reason for the low requirement of calcium and adequate retention of both by Chinese women during pregnancy.

Osteomalacia is now an uncommon disease in women of childbearing age in Europe and there are very few recent references in the literature. A case of osteomalacia was described by Kenny in 1941 (419). This woman, 22 years old, was a native of the Punjab district of India but for 7 years had lived in England. Her first pregnancy, in 1936, was uncomplicated and resulted in the delivery of a normal, full-term, living child. The second pregnancy, in 1939, was accompanied by pain in the extremities which dated from 4 months prior to conception. At the tenth week of pregnancy marked osteomalacic deformity of the pelvis was detected. The infant, delivered by Caesarean section, was fed vitaminized dry milk from birth but showed active rickets when 6 months old. The first child on examination when $3\frac{1}{2}$ years old was underweight and showed marked dental caries and X-ray evidence of healed rachitic lesions of the tibiae, although feeding in infancy had been with vitaminized dried milk. Unfortunately, information about the mother's diet was not available. Mellanby (558) and the Toveruds (884) emphasized that a tendency to rickets is not removed by a period of good diet and may become evident later.

In 30 years only one case of osteomalacia (519) has been reported from the Royal Maternity and Woman's Hospital in Glasgow. A woman 29 years old was admitted

with antepartum hemorrhage in the thirty-seventh week of her fifth pregnancy during seven years. The outcome of one earlier pregnancy had been miscarriage and of another, stillbirth. The complaint on admission was stiffness and extreme pain in legs and feet. The pelvis was so deformed that a stillborn and partly macerated child was delivered by Caesarean section. The serum calcium was 10.0 mg. per 100 ml. of plasma, inorganic phosphorus 1.6 mg., and plasma-phosphatase 7.7 Bodansky units. Rarefaction of the long bones also was noted. The patient had had stiffness of her hip joints for 5 years, most marked during pregnancies. Her diet had consisted chiefly of fried potatoes, meat, and occasionally fish. The author considered peculiar the fact that in a district with a relatively common finding of rickets, osteomalacia should be so rare.

The foregoing case illustrates the fact that in pregnancy inadequate diets usually produce multiple deficiencies rather than deficiency of only one nutritional factor. Of the patient's earlier pregnancies, one had ended in miscarriage and stillbirth; the reported delivery was preceded by antepartum hemorrhage, the pelvis was severely deformed, and stillbirth was the result. All these are just expressions of multiple deficiencies in a body depleted by the demands of reproduction and never replenished owing to poor food habits and to lack of knowledge and of economic resources.

Balance experiments have provided deeper insight into calcification processes. Jeans (407) found that, with irradiated cow's milk as the sole source of vitamin D, an average of 90 units daily over the period of infancy seemed to be sufficient to prevent clinical rickets in the average infant and to permit average growth and development but was not considered as optimum, even for full-term infants. Jeans and Stearns (408) then showed that milk containing 300 to 400 units of vitamin D per quart gave greater mineral retentions and skeletal growth, with earlier dentition. If the amount of vitamin D ingested was markedly increased—up to 1500 or more units daily—evidence of decreased appetite and retardation of growth began to appear at or beyond 6 months of age. Decreasing the intake resulted in an increased rate of skeletal growth within 2 months. Infants fed human milk also showed increased mineral retention and increased rate of growth when additional vitamin D was given.

One-third of the skeletal minerals are normally deposited during the last month of pregnancy, so the skeleton of an infant 4 weeks premature is only about two-thirds as well calcified as that of the full-term infant. Davidson and associates (179, 180) found that irradiated evaporated milk (135 I.U. per liter) did not prevent moderate or severe rickets in premature infants, whereas 400 or more units to the quart of cow's milk was effective. For the best growth, about double the amount needed for full-term infants is considered by Stearns (815) to be adequate for premature infants, while Glaser *et al.* (1008) have shown that premature infants need no more vitamin D than do full-term infants.

Almost all pediatricians agree that addition of vitamin D to a cow's-milk formula is desirable. Many have hesitated to advocate vitamin D supplements for breast-fed infants because human milk is considered nature's complete food. However, the composition of breast milk varies with the diet of the mother and with exposure to

sunlight, which is hampered by clothing. In addition, vitamin D does not readily pass into the human milk even if the mother's intake is very high. Clausen (131) stated that mothers given a good diet with addition of 300 to 600 I.U. of vitamin D daily did not have more vitamin D in their milk than 7.5 I.U. per 100 ml. The average vitamin D content of human milk is 5 I.U. per 100 ml., so a daily milk flow of 1000 ml. would not provide more than 50 I.U.

Since the requirement of breast-fed infants for vitamin D is, in general, less than that of babies fed cow's milk, infants fed human milk are less liable to develop rickets when vitamin D is not given. However, Clausen (131) reported that at an infant welfare center in Copenhagen 35 per cent of the infants with rickets were breast fed. Madsen (529) has found severe forms of rickets in infants fed human milk exclusively until they were 4 to $4\frac{1}{2}$ months old. From Norway, a report (903) stated that 33 per cent of 185 infants showing deviation from normal calcification, mostly in the form of craniotabes or bowing of the legs, were exclusively breast-fed infants. Addition of vitamin D is generally recommended for all infants after the first month of life (131, 226, 409, 903). In northern Europe addition of vitamin D throughout the summer season (903) seems to be necessary also because the amount of sunshine is so variable that in some years exposure may be minimal.

Garry and Wood (279) question the desirability of increasing the rate of growth in infancy when nature has provided the vitamin D growth factor so meagerly in our common food articles. Jeans and Marriott (409) state that cod liver oil or other suitable form of vitamin D should be given in the first 2 weeks after birth and the dose increased as rapidly as possible until the intake is 300 to 400 units per day. The more concentrated forms of vitamin D are less efficiently utilized, and when these are given the intake should be increased to 600 to 800 units daily. In recent years massive doses of vitamin D have been administered for prophylaxis. Some infants and children who have died (409) after such therapy have shown calcification of various tissues and extreme renal damage.

VITAMIN A

Of the two chemical forms (409) of vitamin A, vitamin A_1 is found as a fat-soluble, colorless factor in animal products such as milk, eggs, fish oils, and fish liver oils. Vitamin A_2 has been found only in fresh-water fish and apparently is of minor importance. A number of vitamin A precursors, carotenoids, whose chemistry has been reviewed by Rosenberg (724) are especially important. Of interest in human nutrition are alpha, beta, and gamma carotene and cryptoxanthin, which previously were thought to be absorbed in the presence of bile as water-soluble compounds (202), carried to the liver where they were stored, and finally converted into vitamin A under the action of the enzyme carotenase (459). Recently, this conversion has been found to occur in the intestinal wall (547, 975). These provitamins which give the yellow color to many fruits and vegetables and are present in association with chlorophyll are less efficiently utilized than vitamin A. The esters of the vitamin A in natural foods have a greater biological activity and are more stable than the free form found in the non-saponified fractions and concentrates. Vitamin A is stored

in the liver, the amount depending on intake and the physical condition of the individual (227).

Vitamin A and carotenoids are absorbed from the small intestine after hydrolysis, and are re-esterfied in the intestinal wall with either the fat carrier or other fatty acids. The rate of absorption seems to be increased when lecithin is fed (409) and in the presence of bile. The peak of absorption occurs 3 to 5 hours after ingestion. Any disturbance of fat absorption and any infection of acute or chronic type will affect the absorption of vitamin A. In infants the absorption of carotene is much less efficient than that of preformed vitamin A. Jeans and Marriott (409) report an absorption of only 40 per cent of carotene in infancy.

Long before vitamins were known, Bitot (59) in 1863 described triangular, round, or oval spots resembling soap foam on the conjunctiva in the palpebral fissure, generally lateral to the cornea. Bitot's spots appear rather late, according to Forest and Wolff (260) 10 to 15 days after the first sign of dryness of the conjunctiva. Nicholls and Nimalasuriya (635) found these spots in children in Ceylon. They started as "small slight thickening and pigmentation of the conjunctiva of the sclerotics," and progressed to a heaped-up accumulation of epithelial cells.

Yudkin (1002) in 1927 described a family of blind albino rats that presented congenital ocular defects and peculiar head malformations, with the eyeball, optic nerve, and chiasm missing. He ascribed these findings to toxic, infectious, or chemical agents transmitted from the mother's circulation to that of the embryo at an early stage of development. The parents and later offspring were normal. Present knowledge indicates that this micro-ophthalmia was probably related to vitamin A deficiency.

Hughes and co-workers (385) in 1928 found that gilts with avitaminosis A showed irregularity in the oestrus cycle, as well as degeneration of the nervous system, characterized by extreme incoordination and spasm. When these gilts were bred, even prior to the onset of nervous symptoms, they aborted or farrowed dead pigs. Conjunctivitis and eye infections were not common, though loss of the senses of sight, smell, and hearing was often noted. Sure (837) and Mason (538) showed that, even with diets containing abundant vitamin E, lack of vitamin A disturbed the oestrus in rats and resorption of fetuses occurred. When young were born they were weak and showed signs of incipient xerophthalmia.

In a dry season in California when fresh green food was scarce Hart *et al.* (342, 343) found that calves were stillborn or weak. Some showed keratomalacia and often succumbed to respiratory infections. Livers from these calves were devoid of vitamin A. Often oestrus failed to return in the cows until green feed was again available. These conditions did not occur when cows were given green food, green food with cod liver oil, or cod liver oil alone.

Mellanby (554, 556, 557, 559, 560) showed that insufficient vitamin A in the diet of growing animals caused: widespread nerve degeneration, more pronounced in some nerves than in others; bone hypertrophy which injures or destroys nerve fibers and nerve cells; and increased susceptibility to infection. Later (561) he found that this hypertrophy could be explained by altered osteoclastic and osteoblastic activity involving all bones of the body. Moore and co-workers (595) described blindness in cattle resulting from atrophy of the optic nerve where it passes through the optic

foramen, apparently due to narrowing of the bony canal and bone pressure as a possible result of vitamin A deficiency.

Hale (326) observed a gilt receiving a vitamin A-deficient diet from 4 months of age. Thirty days after being bred she became too weak to get up. Cod liver oil was given in amounts which enabled the gilt to eat and move around. She farrowed 11 pigs without eyeballs and all died soon after birth. Two years later Hale (327, 328) repeated the experiments with other gilts, first depleting their vitamin A storage, then letting them breed, and continuing their deficiency. In the young a variety of defects was found, including lack of eyeballs, hare lip, cleft palate, arrested ascension of the embryo kidney, and accessory ears. Even in the offspring of a gilt given cod liver oil 2 weeks before conception and another given vitamin A after the first weeks of gestation these changes occurred.

From experiments with rats, Warkany and co-workers (942, 943, 944, 947, 950) described various malformations resulting from vitamin deficiency. In one study cleft palate occurred in 44 per cent of the abnormal specimens. Deformities of the tibia, mandible, ribs, and other parts were more frequent. Some of these malformations resulted from a shortage of riboflavin. In one investigation (950) female rats were given a diet deficient in vitamin A, which contained only enough carotene to make growth and maturation possible but prohibited storage of vitamin A. At maturity the rats were given a diet completely free of carotene and vitamin A and later were bred to normal males. Within 1 or 2 weeks the mothers showed signs of vitamin A deficiency and their young presented various defects of the skeleton and soft tissues, particularly of the eyes: colobomas, eversion and abnormal structure of retina, rudimentary development of the iris and of the ocular chambers, and defects of the cornea and of the conjunctival sac. Many fetuses 15 to 16 days old could be recognized externally as abnormal. When the maternal diet was supplemented with vitamin A during pregnancy the eyes of the young were normal.

Richardson and Hogan (705) found hydrocephaly in 2 per cent of offspring from rats receiving a synthetic diet containing all vitamins except ascorbic acid and B_c. The authors considered this abnormality a result of a nutritional deficiency of unknown origin. Dann (167, 169), in experiments on rats and rabbits, found evidence that small amounts of vitamin A, or materials from which it can be synthesized, are transmitted from mother to offspring, either through the placental barrier or in the mother's milk, with little quantitative variation in the small amount so transmitted.

Such extreme deficiencies as those cited above are not seen frequently in human beings, but animal experiments have emphasized the value of vitamin A storage in the maternal body for the development of the fetus. Regardless of the causes of depletion—poor diet, starvation, defective absorption, infection, or other debilitating processes—the losses should be replaced prior to pregnancy. At the time a pregnant woman seeks medical advice, fetal damage may already have occurred if her previous diet, utilization, or general health has been poor.

The Food and Nutrition Board, National Research Council, has recommended a daily intake of 6000 I.U. of vitamin A during pregnancy, based on the premise that approximately two-thirds of the vitamin A value of the average American diet is contributed by carotene and that carotene has half or less than half the physiologic

value of vitamin A. For the latter half of pregnancy the recommendation is 6000 I.U. This amount can easily be furnished in the diet by 3 pints of milk, or by butter or fortified margarine, eggs, and plenty of leafy and green vegetables, and an adequate intake is assured by provision of 5000 I.U. as cod liver oil or its equivalent daily throughout pregnancy.

The vitamin A storage at birth reported from different countries varies widely, perhaps owing to differences in maternal feeding as well as in analytical material available. The values reported for newborn infants range from 25 to 1040 I.U. of vitamin A per gram of liver (294, 478, 863, 891, 958, 990). Both the hepatic cells and Kupffer cells seem to store this vitamin (151, 678). Lasch (459) provided best evidence that storage occurs in Kupffer cells. In later infancy (227) the store in the liver increases and reaches a rather static level during the latter part of lactation. Prematurely born infants have a smaller store of vitamin A in the liver than do babies born at term (409).

Moore (598) found 290 I.U. of vitamin A per gram of liver from adult human beings. Wolff (990) found only 42 I.U. per gram of liver in newborn infants, with hardly any difference between full-term (44 I.U. per gm.) and premature infants (41 I.U. per gm.). Three years later a similar study by Toverud and Ender (890) showed an average of 39 I.U. for full-term and 65 I.U. per gram for premature infants. The content varied from one infant to another, in close relation to the diet and health of the mother during pregnancy. In a group of infants whose livers showed vitamin A contents ranging from 0.1 to 3 I.U. per gram, the diets of the mothers had been very low in vitamin A. The liver of an infant whose mother had ingested a diet containing a large amount of vitamin A contained 310 I.U. per gram. Lewis *et al.* (478) among 20 newborn infants found 1 and 3 I.U. of vitamin A per gram of liver, respectively, for one premature infant and one full-term infant born of a mother who had had obstructive jaundice for 3 weeks prior to delivery. In the livers of the other infants the range was 16 to 507 I.U. of vitamin A per gram, with a mean of 115 I.U. Diet histories were not given.

The vitamin A content of the livers of pregnant women has not been investigated, but many studies of the blood in pregnancy have been reported. Wendt (958) found that 15 per cent of pregnant women in Germany had very low blood vitamin A in the last part of pregnancy, with hardly any store in the placenta. He also noticed that the content of cord blood was far below that of pregnant women and that the vitamin A content of the newborn infant's liver decreased towards term. Gaehtgens (271) also found that the fetal liver showed a decreasing content of vitamin A and carotene towards term, and later (272) found the placenta to vary in its vitamin A content according to the diet of the mother. Lund and Kimble (493) also found that blood serum vitamin A is lower near the end of pregnancy.

In London, Hoch and Marrack (363) found the mean serum vitamin A concentration to be lower in pregnant women than in non-pregnant women, a finding which reflected the dietary intakes of vitamin A, and to be generally low in women who had not received prenatal care. Lund and Kimble (494) also found that puerperal morbidity and complications of pregnancy and labor were less frequent when plasma levels remained above 90 I.U. per 100 ml., which recalls the results of Mellanby and

Green (555) in successful treatment of human puerperal septicemia with vitamin A concentrate. Maxwell (548), from observations of women in China, also believed that vitamin A deficiency might play a role in the etiology of puerperal sepsis and reported the case of an infant actually born with keratomalacia, which he attributed to insufficient vitamin A in the mother's diet. A similar case in Holland was reported by Van Creveld (919), showing that this condition actually existed in Europe before the war.

Menken (572) found 48.7 per cent of infants studied had no detectable vitamin A in their cord blood. Gaehtgens (270) reported traces of vitamin A in 26 samples of cord blood. Clausen and McCoord (132), however, found substantial amounts of carotene and vitamin A in fetal blood but were of the opinion that values were not high enough to suggest ready transfer of vitamin A across the placental barrier. Byrn and Eastman (106) also found substantial amounts of vitamin A in cord blood, averaging 91.3 I.U. per 100 ml., with a corresponding average maternal level of 106.3 I.U. a few hours before delivery. In 10 cases the fetal level was far above the maternal, and of 50 cases only 11 showed a fetal level below 70 I.U. per 100 ml. of plasma. No carotene could be detected in 28 samples and only traces in the other 22 samples of cord blood, whereas the maternal average was 106.3 mmg. per 100 ml. By feeding 100,000 I.U. of vitamin A daily for a few days before delivery, or every 2 hours during labor, up to 200,000 I.U. during a period of 8 hours before delivery, a sharp rise was produced in the maternal blood but none in the cord blood. They concluded that the problem of placental transfer of vitamin A was still unclear but were of the opinion that the vitamin A gradually stored in the fetal liver had an influence on the level in the fetal circulation. Thus, the vitamin A level in cord blood would be an indication of the liver storage rather than a value closely correlated with fluctuations in the maternal blood vitamin A. Lewis *et al.* (479) found that the drop in vitamin A content of the mother's blood in the last trimester of pregnancy might be prevented by giving large amounts of vitamin A (10,000 I.U.) daily. The vitamin A and carotene values of cord blood, however, were no higher in the infants of those women than in cord blood of infants whose mothers received no supplements.

These results seem to indicate a marked limitation of the placenta in transmitting vitamin A to the fetus, but in view of the studies (890) which showed more vitamin A in the livers of newborn infants whose mothers had had good vitamin A-containing diets, it is plausible that considerable amounts of vitamin A may pass into the placenta without increasing the levels in the cord blood; however, the store in the liver may rise and thus regulate the level in the cord blood. The fetal liver may withdraw vitamin A from the blood so efficiently and so rapidly that transmission of the substance through the placenta is not reflected in increased concentration in the blood of the newborn.

Lund and Kimble (493) found 24 to 79 I.U. of vitamin A per 100 ml. of blood plasma at birth, independent of the maternal values; carotene, however, varied regularly with the level in the maternal plasma. Lewis *et al.* (478) found the lowest level of vitamin A in the blood of 144 normal infants to be 45 I.U. per 100 ml. Lower values were determined for infants receiving diets devoid of vitamin A and others with disorders affecting the absorption of fat. Low levels of vitamin A in the blood were

associated with poor dark adaptation and with low storage of the vitamin in the liver. Daily administration of 17,000 I.U. of vitamin A to infants during their first 6 months of life produced increases in vitamin A in the blood. However, no appreciable effect on the level of vitamin A in the blood was noted with infants 6 to 18 months old who were given vitamin A daily for 1 to 5 months. These authors found a high incidence of poor dark adaptation and low levels of vitamin A in the blood during febrile diseases. In febrile infants, administration of vitamin A concentrates brought a rise in blood level in 24 to 48 hours.

Henley *et al.* (350) also concluded that the plasma vitamin A content was related to intake and unrelated to birth weight. Their average for premature infants not receiving supplements was 68.4 I.U. per 100 ml. About one-fourth of the infants, however, at 3 weeks of age had levels below the 45 I.U. per ml. of plasma, which has been considered an acceptable minimum value. They concluded that early supplementation of premature infants' diets with concentrates containing vitamin A is a desirable routine procedure.

The source of vitamin A in the first weeks and months of life is human milk or cow's milk. All authors seem to agree that colostrum of women contains 2 to 3 times, and of cows 10 to 100 times, the amounts found in the respective mature milks (528). Vitamin A in mature human milk varies from 200 to 300 I.U. per 100 ml. when the vitamin A intake is 50,000 to 100,000 I.U. daily (467). Human milk has been reported (171) to contain as much as 14 times as much vitamin A and 6 times as much carotenoids as cow's milk, but such differences do not always prevail. Values for vitamin A and carotenoids in human colostrum and mature human, goat, and cow milks are included in the summary (Table 16) of a comprehensive compilation of original data on milk composition (528).

Pasture-fed cattle yield milk containing more vitamin A than that from stall-fed cattle. The Medical Research Council of Great Britain (552) has accepted 140 I.U. per 100 gm. as a mean value for the summer season and 70 I.U. per 100 gm. as a representative average for the winter season. Lawrence *et al.* (461) give as mean values from 12 different investigators: 33 mcg. of vitamin A and 30 mcg. of carotene per 100 ml. of milk. If 0.25 mcg. of vitamin A and 0.6 mcg. of carotene are each considered as equivalent to 1 I.U. of vitamin A activity, the average potency for milk would be 182 I.U. per 100 ml., with 50 per cent more in summer milk (270 I.U.) and 50 per cent less in the winter (90 I.U.).

The vitamin A intake of an artificially fed infant varies with the milk and with season; according to Clements (135) it may vary from 400 to 1400 I.U. With 90 I.U. in 100 ml. of milk, cow's milk diluted one-half or one-third might not provide more than 300 to 400 I.U. of vitamin A per day to an infant in the first weeks of life. Even a liter of undiluted milk might not contain more than 900 I.U. The vitamin A intake of a breast-fed infant would be 2000 I.U. daily from 800 ml. of milk with a mean content of 250 I.U. per 100 ml.

The requirement for vitamin A in infancy is unknown but the levels have been determined in blood, and dark adaptation tests have been used. The adult requirement has been estimated at 20 I.U. per kilogram of body weight as a minimum and double that amount when given as carotene. Jeans and Marriott (409) estimate on this basis a storage requirement 3 times the minimum one, or 60 I.U. per kilogram.

Doubling the amount for infancy makes a total of 120 I.U. of vitamin A or 240 I.U. as carotene per kilogram body weight as a complete requirement. The National Research Council's allowance is 1500 I.U. daily for an infant under 1 year of age, an amount a breast-fed baby usually receives from the milk. An artificially fed infant may have a low intake in the winter. Both Lewis and co-workers (478) and Henley and his group (350) found that early supplementation of the diet with vitamin A was desirable for both full-term and premature infants, based on the blood studies. Jeans and Marriott (409) consider the usual milk dilutions sufficient without supplementation. After 4 months of age the addition of vegetables, fruits, and egg yolk may enrich the diet with so much vitamin A that supplementation may be superfluous.

When vitamin A deficiency is severe, the deeper layers of the cornea change so that cloudiness appears, leading to an opaque structure and, in young infants, with further development to softness and perforation. This xerophthalmia developing into keratomalacia was described by Thalberg (859) in 1883 in breast-fed infants whose mothers were fasting. These cases usually appeared at the end of March after the long fast. Later, xerophthalmia and keratomalacia in various parts of the world were described. Osborne and Mendel (648) and McCollum (509) found this condition in their animal experiments. Bloch (64, 65) clarified its etiology with Danish infants during the First World War, and Blegvad (63) found total blindness in 27 per cent of 298 Danish infants who survived kerotomalacia during 1909 to 1920, and greatly impaired vision in 24 per cent of the children. Schwartz also reported a case (749) in which blindness resulted. De Haas and co-workers (324) reported 20 to 30 per cent occurrence of blindness after xerophthalmia in Batavian children. From experience the cornea is more vulnerable in infants than in older children and adults, which would explain the rare occurrence of keratomalacia in adults.

Changes in the eye are the result of primary damage to the epithelial cells of the cornea, followed by formation of stratified, keratinized epithelial tissue, from which arise numerous pathologic conditions. According to Bessey and Wolbach (54) the trachea and the bronchi are the most common sites and the points of earliest appearance of keratinizing metaplasia in human infants, rendering these mucous membranes rather susceptible to bacterial invasion. In Blegvad's (63) series, a large number of the fatalities were due to respiratory disease. In vitamin A deficiency in infancy, respiratory complications were noted frequently among the 13 cases described by Blackfan and Wolbach (61), by Thalberg (859), and by Sweet and K'ang (847), who studied 30 Chinese infants of whom 22 were less than 6 months of age. Blackfan and Wolbach (61) called attention to the fact that cornified epithelial cells appear where they do not normally occur, in the nose, trachea, kidney, and vagina, after bodily stores of vitamin A are completely exhausted and vitamin A is absent from the blood.

Changes may also take place in the epithelial cells of the skin of infants (64, 65). The skin was described as dry and scaly over the shoulders in an infant 55 days old. In a 16-day-old infant the skin was scaly with sharply pointed follicular papules on the upper extremities, the trunk, and in the axillary folds. In an infant 69 days old the skin showed hyperkeratosis (64). One hair follicle contained a keratinized spine which extended beyond the mouth of the follicle, and other follicles showed considerable hyperkeratosis without spine formation. There was no perifollicular hyperkera-

tosis with distension of the follicles. These changes, called phrynoderma, seem to be more common in adults than in infants.

The earliest symptom of a vitamin A deficiency seems to be diminished vision in dim light. It is well known that vitamin A is necessary for the regeneration of the bleached pigments of the retina to the original visual purple. It is reported by Holcomb (369) that nightblindness was known and the beneficial result of a liver diet in its treatment was described by Paul of Aegina in 500 B.C.

The next phase in vitamin A deficiency is a lowering of the blood content of vitamin A. May and co-workers (550) found that the carotenoids disappeared from the blood first and then the vitamin A level was reduced. The carotenoids were evidently withdrawn from the blood to the liver for conversion into vitamin A. When the vitamin A as well had disappeared from the blood, cornified epithelial cells appeared.

From study of the vitamin A and carotenoids in blood, May and his group (550) followed the gradual depletion of the body of a prematurely born infant one month old while receiving a formula containing a small amount of vitamin A. Vitamin A and carotenoids were measured in "units" expressing relative extinction determined in a standard cell with an Evelyn colorimeter. The premature infant was admitted to the hospital with a vitamin A level of 1.1 units per 100 ml. Clinical evidence of vitamin A deficiency was not present. By giving carotene in oil the levels of carotene and vitamin A in the blood were raised to high levels after 11 days. After the bodily stores had been replenished, the infant was given only an evaporated milk formula estimated to contain 600 I.U. of vitamin A per day, increasing to 1800 I.U. as more milk was consumed. After 19 days of this diet the levels of vitamin A and carotenoids fell to 8.0 and 12.8 units, respectively, per 100 ml. of blood. The vitamin A level remained at 8 units while carotenoids continued to decrease. After 3 months, when the carotenoids had dropped to 7.2 units, the level of vitamin A began to fall. Thus, the fall in vitamin A was delayed for 3 months while the carotenoids were being depleted to help maintain the level of vitamin A in the blood. When the carotenoid level became extremely low the vitamin A level fell in spite of the intake of vitamin A provided by the milk. During this 3 months of chronic depletion the infant enjoyed robust health and had increased from $4\frac{3}{4}$ pounds at birth to 16 pounds at 5 months of age. This and similar experiences with full-term infants cause the authors to state that: "the amount of vitamin A customarily supplied to infants in ordinary whole cow's milk formulas may be scarcely sufficient to maintain an optimal level of vitamin A in the blood."

The studies reported seem to show that human milk under ordinary conditions supplies the infant's need for vitamin A. Ordinary cow's milk formula may, before any other addition is made to the milk diet, require supplementation of carotene or vitamin A. Kennedy and co-workers (417) as early as 1923 found that human milk in its content of vitamin A was superior to cow's milk and that the content was dependent on the mother's diet. Macy and collaborators (512, 521, 522, 649) pointed out the differences between cow's milk and human milk, the variations in composition of milk from individual women, and the effect of vitamin A addition to the diet. In all milk studies the technic of collection of the samples is of great importance because the concentration in the first milk expressed is considerably different from that in

the last part (121, 171, 467, 620). Lesher *et al.* (468) found that all women examined showed similar patterns of secretion of vitamin A and carotenoids in the milk. During the puerperium small amounts of vitamin A were secreted in the first 2 days postpartum, followed by large increases in the third or fourth day, and reduced values after the sixth day. Carotenoids were relatively higher on the first 2 days, increased to a peak on the third and fourth days, and decreased rapidly from the sixth to tenth day. In mature milk, vitamin A ranged from 0.13 to 0.60 mg. per day. The amounts of the vitamin paralleled the values of milk secreted and were not related to intake within the limits of variation in the diets of the women studied. Estimating that one-fourth of the carotenoids in the milk was carotene, the total vitamin A activity of the milk was 0.56 to 1.24 mg. during the first 2 days postpartum and 0.14 to 0.64 mg. per day during periods of secretion of mature milk.

Regular ingestion of cod liver oil during pregnancy (171, 512) was not found to increase the vitamin A content of colostrum. When, however, 50,000 I.U. was given to the mother as a supplement (468) an appreciable increase in the vitamin content of the milk was found. Friderichsen and With (266) found that 2 to 10 mg. of carotene added to the diet increased the content in the serum but not in the milk.

VITAMIN C

The exact functions of vitamin C in the body are not fully understood but it plays an important part in all growth processes and is found in abundance in active, growing tissues. Vitamin C evidently has a role in respiration and other functions pertaining to regulation of the colloidal condition of intercellular substance in cartilage and bone, the collagen of all tissues (153, 154, 368, 391, 491) and the function of the osteoblasts. The term ascorbic acid is currently in general use for vitamin C, but upon oxidation ascorbic acid loses 2 hydrogen atoms to form dehydroascorbic acid. Since some analytical methods determine only ascorbic acid but others determine ascorbic acid plus dehydroascorbic acid, determinations of ascorbic acid only may not provide true estimations of the original vitamin C activity of the sample analyzed.

The distribution of ascorbic acid varies in the body from one organ to another (53) with the highest contents, 140 to 230 mg. per 100 gm. of substance, in the adrenals and corpus luteum. Placentae have been reported by various authors (107, 380, 588, 607, 621, 624) to contain from 4.9 to 39.1 mg. of ascorbic acid per 100 gm., distributed (588, 622, 623) in varying amounts among the syncytium, the decidua, and the stroma cells. The most active metabolism of vitamin C occurs in the cells of the placenta villi (751) and Tonutti and Plate (877) pointed out that the loading of the Golgi apparatus with vitamin C, such as is found in the placenta, is characteristic of an organ through which the vitamin is "passing," in contrast to an organ in which it is "stored." However, some ascorbic acid is evidently stored in the body, for in human beings scurvy may not develop until months after the vitamin has been withdrawn from the diet.

Ascorbic acid is excreted in the urine and feces, mainly through the kidneys, depending upon the intake. Abbasy and co-workers (1) consider a daily urinary excretion of 20 mg. to represent a moderately low intake, and of 40 mg., a liberal intake. The excretion in infants is much less, values of 5 mg. and below being found in the urine (187). Attempts to judge the normal requirement under various conditions by

the levels of ascorbic acid in the urine after fasting, after the usual diet, and after saturation doses of ascorbic acid, have not been conclusive.

The Food and Nutrition Board, National Research Council, recommends 100 mg. of ascorbic acid per day during pregnancy. Excretion tests have shown that a high intake is needed to keep the excretion during pregnancy at the level of non-pregnant women but such an intake is very difficult to achieve in some countries, particularly during the winter season, and scorbutic symptoms do not develop even with intakes 50 per cent lower. Clinical symptoms, however, occur at a late stage in the development of a deficiency, and further research must establish the minimal level for health.

The manifest deficiency, infantile scurvy, originally described by Barlow (38, 39, 40) is now uncommon in civilized countries but congenital scurvy occasionally has been reported. Scurvy in a 20-day-old infant was described by Jackson and Park (402) but more commonly occurs between the ages of 7 and 12 months in infants whose parents are well-to-do but careless, while almost never appearing among the poor. Hess (353) was the first to draw attention to this mild form, the symptoms of which are failure to gain weight, irritability, and poor appetite. Changes found by X-ray studies of the bones were described by Park and co-workers (652). Mild scurvy usually occurs in artificially fed infants who have not received vitamin C supplements.

Most authors agree that there is a significant relationship between the dietary intake and the plasma level of ascorbic acid. Todhunter and Robbins (875) found for three adults that the blood contained 1 mg. of ascorbic acid per 100 ml. of plasma when the total daily intake was 60 mg. When the intake was raised to 120 mg., levels in the plasma reached 1.4 mg. per 100 ml. The desirable level of ascorbic acid in the blood of an adult, however, is not known, and evaluation of analytical results is hampered by the fact that some methods provide higher values than do others.

Moore *et al.* (596) studied the blood of 159 pregnant women, of whom 90 were white and 69 Negro, and determined averages of 0.46 and 0.31 mg. per 100 ml., respectively, of plasma. Considering 0.60 mg. or above as "normal," only 26 per cent of the white group and 12 per cent of the Negro group showed such values. Hamil and associates (330) found in maternal serum from 0.04 to 1.19 mg. of vitamin C per 100 ml., with great variations in individual women. Values at different times in pregnancy were given by Teel and Ingalls and co-workers (858, 393):

Mean Vitamin C Levels in Maternal Blood Plasma (393, 858)

mg. per 100 ml.

Vitamin C intake*	Period in pregnancy				
	First 28 weeks	29th–40th week	At delivery	Cord	2 weeks post-partum
Normal or above	1.04	0.89	0.88	1.77	1.44†
Suboptimal	0.66	0.45	0.44	1.19	
Deficient	0.29	0.19	0.24	0.89	0.30

* "Normal or above" designates a daily diet estimated to contain at least 50 mg. ascorbic acid. The term "deficient" connotes less than half the "normal" amount.

† Patients received a daily supplement of 300 or 600 mg. ascorbic acid in addition to the 20 mg. in the usual diet.

In a group of 1091 pregnant Norwegian women, 2794 blood tests taken at various stages of pregnancy showed figures from 0.49 to 1.06 mg. per 100 ml. (903). The women were supervised, but diet was restricted by the war situation. Decreasing values throughout the years of food rationing are seen in Figure 6.

Ascorbic acid seems to be transferred from mother to fetus in a different manner than the fat-soluble vitamins. Teel and co-workers (858) found that with a relatively constant intake of vitamin C the amount of ascorbic acid in maternal blood plasma decreased markedly as pregnancy advanced, whether the dietary intake of vitamin C was optimal, suboptimal, or deficient. The average amount of ascorbic acid in maternal plasma at the time of delivery was only slightly more than one-half that present during the first 28 weeks of pregnancy (0.47 and 0.72 mg. per 100 ml., respectively). The mean amount of ascorbic acid in plasma from cord blood was 2 to 4 or more times greater than that in maternal plasma taken at the time of delivery (858). The greatest differences were found when the values for the maternal blood were lowest. In the plasma of 3 patients with severe and prolonged hyperemesis gravi-

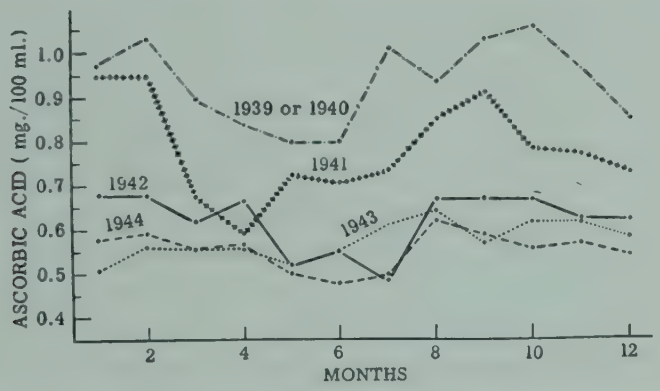

Fig. 6. Average Ascorbic Acid Content of the Blood of Pregnant Women (903)

darum the ascorbic acid contents were 0.2 mg. or less of ascorbic acid per 100 ml. One of these patients showed clinical scurvy which responded promptly to therapy.

Snelling and Jackson (799) found a slight fall in plasma ascorbic acid toward the end of pregnancy. They also found a higher ascorbic acid level in fetal blood than the level in maternal blood, which has been verified by many authors (228, 229, 495, 588, 624). Only a few cases are recorded in which the vitamin C level in the maternal blood is equal to or higher than the level in the fetal blood (255, 935). Lund and Kimble (495) are of the opinion that the higher level in the fetal blood results from the selective permeability of the placenta, contrariwise to the findings for the fat-soluble vitamins. If this is true the maternal tissues of many women may lack vitamin C during pregnancy. Gaehtgens and Werner (273, 274, 275, 276) claim the incidence of such deficiencies to be 50 to 75 per cent.

The blood of newborn infants also has a considerably higher content of ascorbic acid than the maternal blood (584, 935). Manahan and Eastman (531) found a mean value for plasma ascorbic acid in newborn infants (premature and full-term) of 1.15 mg. per 100 ml. and of 0.38 mg. in mothers. (On the fetal side of the placenta the concentration was about three times its concentration on the maternal side, again pointing to selective placental permeability.) Whether rather high blood levels indi-

cate good ascorbic acid reserves is not known. The high levels at birth seem to decrease immediately. In the infants studied by Mindlin (584) the average umbilical blood plasma level of 1.2 mg. per 100 ml. fell to 0.7 mg. the third day after birth and thereafter was determined by the type of food given to the infant. Braestrup (74) found a drop from 0.69 to 0.27 mg. per 100 ml. plasma during the first 10 days after birth.

The ascorbic acid content of human milk has been found to range from 1 to 11 mg. per 100 ml. (45, 75, 228, 273, 274, 275, 276, 280, 393, 899, 931, 970). Breast milk from Danish women was found by Braestrup (74) to contain from 2.2 to 6 mg. of ascorbic acid per 100 ml. Elmby and Becker (229) studied the milk of a mother receiving a diet high in ascorbic acid and found it contained 6 times the amount of ascorbic acid found in milk of mothers with low intakes. Ingalls and co-workers (393) found 11.6 mg. per 100 ml. in human milk after giving massive doses of vitamin C orally and intravenously. Their usual hospital diet resulted in an average ascorbic acid content of 4.5 mg. per 100 ml. during the first 2 weeks of lactation. When a liberal amount of ascorbic acid was added to the mother's diet the content increased to 7.3 mg. per 100 ml. Munks and co-workers (610) found 7.2 mg. per 100 ml. the first 10 days and an average of 5.2 mg. per 100 ml. in mature milk.

An average figure of 3.9 mg. per 100 ml. was found in 75 analyses of human milk in Norway just prior to the war (899) when the mothers had a daily intake of about 75 mg. of vitamin C. When the intake was raised to 100 mg. the milk content averaged 5 to 6 mg. per 100 ml. In a woman with symptoms of scurvy the content 6 weeks after delivery was 0.41 mg. per 100 ml. During the years of war (903) the analysis of the milk from 526 mothers demonstrated that the milk of 145 (28 per cent) had less than 3 mg. per 100 ml. The ascorbic acid of the diet varied but usually did not exceed 75 mg. daily. During the same years 40 per cent of the blood samples from 2216 lactating women showed less than 0.6 mg. of ascorbic acid per 100 ml. In a few instances some bleeding from the gums was noticed but no other symptoms of scurvy developed.

Fresh cow milk usually contains not more than 2.0 to 2.5 mg. of ascorbic acid per 100 ml. (461). The milk which the consumer receives usually contains only a small percentage of this. Losses of vitamin C between the time the milk leaves the cow and the time it is used are much more important than variations in the fresh milk (461). Much of the market milk as used was found by Sharp and co-workers (761) to contain practically no ascorbic acid. According to Hand (334) general exposure of the milk to light is the most important cause of loss. Reconstituted evaporated milk, according to Jeans and Marriott (409), may contain approximately 0.6 mg. per 100 ml. and dried milk possibly 1.2 mg. per 100 ml.

Values recently compiled (528) showed that the ascorbic acid content of the secretion from the human breast 1 to 5 days postpartum ranges from 0.4 to 10.4 mg. per 100 ml. and 6 to 10 days postpartum, from 2.7 to 9.0 mg. per 100 ml. Data for mature human milk ranged from 0.0 to 11.2 mg. per 100 ml. and for mature cow milk from 0.2 to 3.1 mg. per 100 ml. The summary data from the survey are given in Table 16. The maternal intake of ascorbic acid during lactation recommended by the Food and Nutrition Board (150 mg. per day) should be ample to provide for excretion of milk containing the largest amounts.

The artificially fed infant is almost wholly dependent on supplemental ascorbic acid which is supplied by tomato juice or citrus fruits. Citrus fruit juices are the richest sources of the vitamin, containing an average of 50 mg. per 100 ml. In countries where such fruits are scarce, substitutes must be used: fresh cabbage juice, juice of boiled greens, extract of rose hips, and mashed potatoes, which are important in Denmark for both infants and adults. Turnips, providing approximately 30 mg. of vitamin C per 100 gm., were used extensively during the war as a supplement for breast-fed and artificially fed infants.

The minimal requirement of vitamin C in infants is not known, but Hamil and co-workers (329) estimate it to be about 10 mg. daily. The recommended daily allowance is 30 mg. According to Jeans and Marriott (409), 20 to 50 mg. per day added to the formula of artificially fed infants gives blood levels approximating those of babies fed human milk of average vitamin content.

Many breast-fed infants receive ample vitamin C from the milk, but, since the content is so dependent on the mother's diet, a supplement of vitamin C makes an ample supply certain. Many pediatricians, particularly in northern Europe, have maintained a negative attitude towards such a supplement, partly because "breast milk is nature's food for the infant" and partly because indigestion has been claimed to follow such addition. From 1939 to the present time about 5700 Norwegian infants, of whom 60 to 70 per cent were breast-fed, have been given such additions from about the second week of life without any symptoms of damage (903).

In considering the vitamin C requirement during pregnancy, recognition must be given to the various factors which may influence its metabolism. Spitzer and Shapiro (810) reported that salicylate medication increased excretion of vitamin C by 2 of 7 adults and 9 of 12 children. As an explanation the authors suggest: 1) permeability within the kidney; 2) inhibited reabsorption through the tubular epithelium; 3) formation of a salicylate ascorbic acid compound blocking absorption; 4) competition with the tissues for vitamin C.

Schuck (746, 747) and Cross (155) believe that gingivitis in pregnancy is scorbutic in nature and advocate massive doses of ascorbic acid as treatment. Kutzleb (454) also found that gingivitis and vulvitis in pregnancy are relieved by administration of ascorbic acid, but not in all instances. They conclude therefore that not all cases of gingivitis during gestation have this etiology. Kutzleb's experience seems to conform with findings in Norway during the war years (903), when gingivitis occurred in pregnant women. Some of these patients were improved by ascorbic acid treatment; however, there was no constant relationship between low content of ascorbic acid in the blood and bleeding from the gums.

Anemia has been universally considered to be associated with scurvy but opinion differs as to the cause and the constancy of the symptom. Hamil and co-workers (329) found that lowering of the hemoglobin level did not appear to be a symptom of mild scurvy, nor was it found to predispose to the development of anemia. Kenney and Rapoport (418), on the other hand, found that administration of ascorbic acid in infantile scurvy caused a rise in red blood cells, the reticulocytes, and the hemoglobin values. There is evidently a difference in the influence of the mild and severe forms of scurvy on the hematopoietic system.

In recent years the relationship of ascorbic acid to some amino acids has been

clarified. Animals given tyrosine seemed to require more ascorbic acid than control animals with small amounts of tyrosine in the diet. When ascorbic acid was absent from the diet homogentisic acid was found in the urine. Addition of ascorbic acid prevented the excretion of this acid (753). Levine and co-workers (474) found hydroxyphenyl compounds in the urine of infants with insufficient amounts of ascorbic acid in the diets. Ascorbic acid addition prevented the excretion of this acid. In later publications (475, 476) they corroborated that the aromatic amino acids tyrosine and phenylalanine are incompletely metabolized by premature infants in the absence of supplements of ascorbic acid. Spontaneous defects evidenced by the excretion of abnormal products in the urine could be eradicated by the administration of ascorbic acid. Full-term infants showed the same reaction when fed pure tyrosine and phenylalanine. Dann (166) studied the ascorbic acid retention in 11 premature infants fed boiled human milk and 11 who received cow's milk formulas. In the infants given human milk, plasma ascorbic acid values of 1.3 to 3.5., averaging 1.9, mg. per 100 ml., were found 4 hours after a test dose of 100 mg. of ascorbic acid intramuscularly or 200 mg. orally. In the premature infants given cow's milk, 0.1 to 1.6, with an average of 0.8, mg. of ascorbic acid per 100 ml. was found. In only 3 infants were values above 1.2 mg. per 100 ml. "The results are interpreted as signifying that premature infants receiving human milk retain a larger part of a 'saturation' dose of ascorbic acid in their tissues than do infants given cow's milk. The hypothesis is offered that an increased daily requirement for vitamin C is related to a high level of protein intake."

Mindlin (583) also found higher plasma ascorbic acid values for breast-fed than for artificially fed infants of the same age (13 to 14 days), 1.0 mg. per cent for the former and 0.3 mg. per cent for the latter. Even with supplements of 75 mg. of ascorbic acid daily, 4 artificially fed infants had values of only 0.6 to 0.8 mg. per 100 ml. Snelling (798) obtained similar results. Holmes and co-workers (370) observed that the low levels persisted for several months. These findings may be the result of the lower ascorbic acid content of cow milk, of a greater need for the vitamin owing to the higher protein content of cow milk, or of individual variation among the infants.

THIAMINE

Thiamine, the pyrophosphoric acid ester (cocarboxylase), is primarily related to carbohydrate metabolism, especially in the cleavage of pyruvic acid. Thiamine alone is ineffective in oxidizing this acid, but in combination with phosphate the reaction occurs. Thiamine being a nutritional factor which has not been shown to be stored in the body, requirements should be met currently by the amounts supplied in food. Thiamine seems to be easily absorbed from the small intestine and is found in the blood chiefly in the form of cocarboxylase. Since thiamine in blood occurs almost wholly in the corpuscles, whole blood values may be misleading.

The requirement for thiamine depends upon the quantity of carbohydrate to be oxidized. Recently, Reinhold and associates (703) found that fat does not have a thiamine-sparing action as was believed formerly, evidently because diets high in fat were usually low in carbohydrate and less thiamine was required for this reason. Discussion of thiamine requirement is hampered by investigators' lack of agreement

on the correct basis for its determination: whether the need is best estimated on the basis of total calorie intake, or non-fat calorie intake, or the relative amounts excreted in urine, with or without loading tests; how long an experimental period is required for good evaluation of requirement, and what constitutes valid evidence of inadequacy. Agreement is fairly general that intestinal synthesis is not a major source of thiamine for the human being.

Williams and associates (979) estimated from diet records that 60 of 91 pregnant women received less than 150 I.U. (0.45 mg.) per 1000 calories in their diets, and about 40 per cent of the group ingested 1 mg. or over daily. Symptoms considered indicative of thiamine deficiency were observed in 30 per cent of the women whose thiamine intakes were low and in only 10 per cent of those women whose thiamine intakes were higher. In a study of 7-day food records kept by 514 pregnant women Williams and Fralin (980) estimated the median intake of thiamine to be 340 I.U. (1.02 mg.) daily. About 28 per cent of the women received between 200 and 300 I.U. (0.6 to 0.9 mg.) daily. Lockhart *et al.* (485) analyzed one-day, self-chosen diets of pregnant women and found the thiamine content varied from 0.24 to 1.61 mg. "Most" of the women received within 25 per cent of the mean value, 1.05 mg. Ebbs and co-workers (212) estimated that the diets of mothers in their low income group contained 324 I.U. (0.97 mg.) of thiamine daily. The literature indicates that in America many pregnant women ingest poor diets containing well under 1 mg. of thiamine daily, and that the "average" intake may approximate 1 mg. daily. The diets of pregnant Norwegian women were estimated to contain 1.5 mg. of thiamine before the war, less during the war years (902).

The use of urinary excretion of thiamine as an indicator of dietary adequacy has serious limitations, since the amount of urinary thiamine excreted from a given intake varies to a considerable extent with the individual (581). Neuweiler (628) determined thiamine in the urine of 40 non-pregnant, 40 pregnant, and 40 puerperal women and found that 26 non-pregnant, 25 pregnant, and 25 puerperal women excreted less than 200 mcg. of thiamine daily; 12, 9, and 13, respectively, excreted under 100 mcg., and 4, 4, and 7 women, respectively, excreted less than 80 mcg. daily. The data did not indicate marked differences among the three groups but 25 to 30 per cent of the women were ingesting less than 1 mg. of thiamine daily if an excretion of 100 mcg. or more can be expected from that intake.

Oldham and co-workers (645) found that pregnant women excreted at least 200 mcg. of thiamine daily from intakes of at least 1 mg., with urinary excretion varying from 19 to 25 per cent of intake regardless of intake level. Siddall and Mull (778) studied the urinary thiamine excretion of 42 pregnant women seen in private practice. The patients had had well-balanced diets which included meat, milk, cheese, eggs, fruit, leafy vegetables, and cereals. Thiamine was determined in 150 24-hour collections of urine. The mean excretion decreased from 286 mcg. per day in the first trimester to 249 mcg. in the third trimester. Addition of 750 or 1500 mcg. of thiamine to the daily diets was followed by marked increases in urinary excretion except by one woman with a twin pregnancy and another with prolonged vomiting.

Toverud found urinary thiamine excretions of 30 to 330 mcg. daily, with a mean value of 80 mcg., in 10 normal, non-pregnant Norwegian women (902). The women

excreted from 2 to 16 per cent of test doses of pure thiamine. The mean daily urinary thiamine excretion of 113 women 4 to 9 months pregnant was 38 mcg. daily, and 52 (46 per cent) excreted no thiamine. Of 10 women living in an institution and receiving a diet considered ample who were given 5 mg. of thiamine, eight did not excrete thiamine in the first 24 hours. In a wartime study (902) the urinary thiamine excretion of 671 pregnant women was determined by the Wang-Harris (940) method. The mean dietary intake was estimated to be 1.3 mg. per day but 33 per cent of the women showed no thiamine excretion, even though all customary precautions were used in collecting the 24-hour urine samples. Many developed neurological symptoms such as numbness in fingers and toes and leg cramps. One woman excreting no thiamine in her urine developed unilateral facial paralysis; after receiving 9 mg. of thiamine daily for 14 days the paralysis disappeared and daily thiamine excretion in urine was 400 mcg. A woman with paralysis of muscles in the right scapular region, who did not excrete thiamine in urine, also recovered after treatment with 9 mg. of thiamine daily. The observed high incidence of symptoms of thiamine deficiency indicates either that the thiamine content of the diet, largely from whole wheat bread and potatoes, was not well utilized, or that the ingestion of small amounts of raw or smoked fish, which is rather common in Norway and was especially common during wartime, caused the destruction of some of the dietary thiamine.

Moore and co-workers (596) studied 159 pregnant Louisiana women whose diets provided average amounts of calcium, thiamine, niacin, riboflavin, and ascorbic acid considerably below the recommendations of the Food and Nutrition Board. Laboratory findings, including hemoglobin, hematocrit, plasma protein, and urinary excretion of thiamine, riboflavin, and *n*-methyl-nicotinamide showed no apparent correlation with dietary intake.

Toverud (902) and Lockhart and co-workers (485) found the response to loading tests of thiamine lower in pregnant than in non-pregnant women. The data of Siddall and Mull (778) indicated a good response of well-nourished women to loading tests, but they observed that multiple pregnancy or excessive vomiting decreased the response notably. Thus studies of thiamine metabolism of pregnant women tend to be confusing, rather than enlightening, as the means of determining thiamine requirement. On the other hand, it is evident that many pregnant women, both in this country and abroad, ingest well under 1 mg. of thiamine daily and far more pregnant than non-pregnant women exhibit signs of thiamine deficiency. Severe polyneuritis (513) appears to occur chiefly after pernicious vomiting, but lesser signs are observed in a considerable number of women during the last trimester of pregnancy, particularly in those whose economic status is low. If one assumes that these women maintain their pre-pregnancy pattern of diet after pregnancy begins, it is obvious that the increase in ingested calories will not provide, *ipso facto*, sufficient thiamine for the demand.

The increase in requirement cannot be estimated with any degree of certainty at present, as it must depend in considerable measure on the thiamine status prior to pregnancy. The practice, prevalent in this country, of providing additional thiamine in the form of medication is probably desirable in cases of long-continued or pernicious vomiting, in cases in which multiple pregnancy is suspected, and if the previous

dietary has been poor. Improvement of nutrition by means of improved diet seems a sounder method of increasing the thiamine intake, both from the nutritional and the economic standpoint. For women whose economic status is low, bread provides a much larger portion of the total calorie intake and thiamine-enriched bread is a means of assuring adequate intakes of that factor. The effect of raw fish on utilization of thiamine should be studied more fully, for smoked raw fish is eaten in considerable amounts in certain sections of this country, and to a much greater extent in northern Europe.

The question of relationship between thiamine deficiency and the symptoms commonly present during gestation has been discussed extensively for 20 years and statements are often contradictory. The uncertainty in diagnosis of thiamine deficiency adds to the difficulty. In a recent report, Salcedo *et al.* (728) found that the "fasting hour" urinary thiamine excretion in beriberi cases is not diagnostic of the deficiency when considered separately from the symptoms and signs characteristic of the disease. However, they found symptoms and signs accompanied by low excretion of thiamine in the "fasting hour" urine specimen, from 0 to 2 mcg., helpful in the diagnosis.

Three symptom complexes during pregnancy have been discussed: first, the general nervous, irritable, fatigued state of mind, accompanied by burning feet, muscle cramps, and palpitation, of which so many pregnant women complain; second, neuritis, with numbness and paralysis; third, toxemia. All investigators have hesitated to consider the neurasthenic syndrome an indication of thiamine deficiency because such symptoms are so frequent that one could believe that a majority of individuals, particularly women, suffer from thiamine deficiency. Nevertheless, experimental studies have shown that such neurasthenic symptoms actually may be the first presenting symptoms of thiamine deficiency. We must, therefore, question whether some of the neurasthenic symptoms seen in pregnant women have an actual relationship to thiamine deficiency when lack of urinary thiamine excretion is so common in pregnancy. Routine determinations of thiamine in the urine of pregnant women might be helpful in interpreting symptoms unexplained by the usual examination.

As early as 1928 Shattuck (762) pointed out that gestational polyneuritis might be a result of thiamine deficiency and 2 years later Wechsler (954) agreed. In 1933, Strauss and McDonald (830) cured such patients by giving the pregnant mothers high-thiamine diets, which Fouts and co-workers (262) and Bryant (90) also were able to do. Bryant considered the extreme weakness and prostration present in the case he described to be a result of a thiamine deficiency acting on the mid-brain. Later, Theobald (869) reported cure of polyneuritis with thiamine, as did Westenbrink and Goudsmit (961, 962). Stähler (812) cured 35 patients with high doses of thiamine daily. At the same time he found that a pregnant woman excreted 30 per cent less thiamine after a saturation test than non-pregnant women did, and that in a polyneuritic pregnant woman who showed a definite deficiency the symptoms disappeared when the thiamine excretion in the urine began to increase.

In 1942, McGoogan (513) summarized the 130 cases of polyneuritis in the literature and added 15. Of the 145, 105 received no treatment and 40 were treated with vitamin B complex. The death rate for the total series was 27.5 per cent, in contrast to 7.5

per cent in the treated group. He advocated early treatment of polyneuritis during pregnancy with thiamine in doses of 50 to 100 mg. daily.

Signs of vitamin B_1 deficiency often are associated with vomiting in the early stages of pregnancy (513, 631, 697, 748) and lack of thiamine has been believed (279) primarily responsible for hyperemesis gravidarum, thus establishing a vicious cycle.

When the edema common during pregnancy has no local explanation, general sources must be sought. It often is combined with albuminuria but may be present without any sign of kidney involvement. Among 1025 pregnant mothers, edema was found present without any local cause in 36 per cent (903). It seems natural to think of a possible relationship between the occurrence of edema and thiamine deficiency.

Many investigators believe that lack of thiamine plays no part in gestational toxemia. Siddall (777), Browne (87), Kappeler-Adler and Cartwright (413) have even predicted that giving vitamin B_1 may be injurious to patients with toxemia of pregnancy. On the other hand, several authors have considered toxemia a result of multiple nutritional deficiency in which that of thiamine plays a dominant role. Theobald (860, 862) advanced the opinion that all toxemic disorders during pregnancy may be regarded as deficiency disease, probably of multiple character. In a later study King and Ride (430) found a striking increase in the incidence of beriberi in Hong Kong during the years 1939 through 1941 with an almost parallel increase in the incidence of pregnancy toxemias, especially eclampsia and preeclampsia, during the same period. The toxemia rate rose from 3.45 per cent during the preceding 3 years to 7.82 per cent during the 3 years under review. Of 371 cases of beriberi complicating pregnancy during this period, 252 cases were also complicated by toxemia; both diagnoses were supported by clinical and laboratory findings. Pyruvic acid in the blood above 0.70 mg. per 100 ml. was found in all but 31 patients, only 2 showing concentrations within the normal limits. The average was 1.17 mg. pyruvic acid per 100 ml. of blood. These studies support the view that a causal relation exists between deficiency of vitamin B_1 and pregnancy toxemia. Prophylaxis and active treatment by administration of vitamin B_1, whether in the form of a thiamine-rich diet or as thiamine supplement, was suggested as the most important single measure in dealing with toxemia of pregnancy.

In European countries the frequency of toxemia decreased during the years of the First World War (792). The incidence was lower than the expected frequency in Holland during the Second World War and in the clinic patients of Utrecht when the food intakes were restricted (792). The general impression of obstetricians was also that the frequency of toxemia decreased during the years of war. Smith (792) believes that acute undernutrition affects a mother and fetus differently than does chronic malnutrition such as has existed for years in Chinese mothers.

Another factor in thiamine deficiency is the lowering of the gastric acidity which Rafsky and co-workers (694) found to take place during severe thiamine deficiency, a finding previously reported by Williams and associates (981) in 4 young women maintained on a low thiamine diet. Low gastric acidity accentuates a nutritional deficiency already present by decreasing cleavage in the intestinal tract, thus inhibiting absorption and utilization of food.

Yeast, a common vitamin B_1 supplement during pregnancy, counteracts the con-

stipation so frequently present in pregnant women, but the thiamine in it may not be absorbed. Parsons and co-workers (656) and Melnick and associates (364, 569) have found that thiamine, free or phosphorylated, does not freely diffuse out of yeast cells and that a large proportion of live baker's yeast cells ingested by man pass through the intestinal tract without complete digestion, probably without rupture of the cell membrane. Whether this is true for brewer's yeast is not known.

Leithauser (464) described 6 cases of abdominal distention which responded dramatically to administration of thiamine chloride and vitamin B complex. Golden (291) previously had pointed out that the intramural nervous system is the most probable medium through which nutritional deficiency affects the intestinal tract. Experimentally, Torda and Wolff (878, 879) demonstrated that thiamine chloride and thiamine pyrophosphate in biological concentrations increase the synthesis of acetylcholine and inhibit it in higher than biological concentrations. They also found that cholinergic nerves liberate not only acetylcholine but also thiamine when stimulated, and that thiamine increases the effect of acetylcholine on the intestine and circulatory apparatus of the cat. Chemically acetylcholine and thiamine chloride are closely related compounds, and hence may function synergistically. It seems probable that these facts furnish clues to the mechanism of production of lowered intestinal motility in the presence of thiamine deficiency and the therapeutic response to administration of thiamine chloride. The often obstinate constipation in pregnant women may thus be a result of thiamine deficiency, yielding to increased thiamine intake (464).

The water-soluble vitamins seem to be fairly readily transmitted in breast milk. The thiamine requirement during lactation is increased, but how much is uncertain. The Food and Nutrition Board recommends 2.0 mg. daily, slightly more than in pregnancy. Roderuck and co-workers (714) found 8 per cent of a mean thiamine intake of 1.1 mg. per day secreted in mature human milk, with an average excretion in the urine of 23 per cent of the intake. The average daily thiamine content of the milk ranged from 30 to 162 mcg. Other thiamine concentrations reported for human milk range from 1 to 25 mcg. per 100 ml. (416, 437, 485, 600, 627, 783, 971). In samples of milk from 17 women Knott (436) found 3 to 18 mcg. of thiamine per 100 ml., averaging 9 mcg. Macy (527) reported a range of 8 to 23 mcg. with a mean of 14 mcg. of thiamine per 100 ml. in 277 samples of mature milk and in a comprehensive survey (528) of data on the composition of human, goat, and cow milks found values ranging from a trace to 32 mcg. per 100 ml., with a mean of 15 mcg.

The rather low secretion of thiamine in breast milk may be the explanation for the rare occurrence of beriberi in lactating mothers, although the disease is found in the Eastern countries of the world and sometimes in other countries. The maternal diet has been shown to be the main source of the amount transferred in breast milk (712). In Norway during the war symptoms of thiamine deficiency in lactating mothers frequently took the form of numbness and local paresis which disappeared after the addition of thiamine to the diet. Lactating women were advised to continue the brewer's yeast usually taken during pregnancy, but the thiamine content of breast milk often was found to be below 3 mcg. per 100 ml. (903). Although the thiamine content of human milk is dependent on the intake of the mother, the level

above which the content cannot be increased, even with excessive doses of thiamine, has been found by some to be about 20 mcg. per 100 ml. (783), and by others to be between 25 and 32 mcg. (600).

The low thiamine content of human milk does not usually result in symptoms of deficiency in infancy. Toverud found that breast-fed infants excrete little, if any, thiamine. Calculated from protein and carbohydrate analyses of Slater and Rial (783) the milk provided 33.2 calories-not-fat per 100 ml. The daily thiamine requirement for metabolism is 82 mcg., using Williams and Spies' (983) factor for the thiamine to non-fat-calories relationship. Assuming 10 mcg. of thiamine per 100 ml. of milk, 800 ml. would provide 80 mcg., just enough to metabolize the non-fat calories in the milk. With less thiamine in the mother's diet, the thiamine content of her milk might be lower. Under such circumstances thiamine excretion in the urine of breast-fed infants hardly would be expected.

Knott (436) found that at low levels of intake artificially fed infants consistently excreted only small amounts of thiamine. With intakes of 80 units or more daily (240 mcg.) thiamine appeared in the urine in large quantities. At intakes above 140 units (420 mcg.) daily the vitamin was excreted in still larger quantities, and it was apparent that more was being fed than the infant needed. Knott concluded that a daily intake of about 240 mcg. of thiamine met the infant's immediate needs and above this level the excess appeared in the urine.

Knott also tried to determine the infant's thiamine requirement from levels of cocarboxylase in infant's blood. Values tended to decrease from 5 or more mcg. per 100 ml. of blood shortly after birth to levels between 3 and 4 mcg. Intakes of approximately 200 mcg. of thiamine daily did not maintain the 5 mcg. of blood cocarboxylase which she considered optimal. Nursing infants had blood cocarboxylase levels between 3 and 4 mcg., and infants receiving manually expressed breast milk showed lower levels of cocarboxylase. The thiamine content of the breast milk evidently was reduced during the 2 to 4 days of storage before feeding. The amount of thiamine furnished by the usual milk formulas, however, did produce levels of 3 to 4 mcg., which Knott believed adequate in the absence of fever or metabolic strain increasing the metabolic need for the vitamin. Slater and Rial (783) suggest that the marginal requirement of the breast-fed infant for thiamine is 0.36 mcg. and the optimal requirement is equal to or less than 0.62 mcg. for each non-fat calorie.

The possibility that thiamine is synthesized in the infant's intestine by bacterial action cannot be excluded. Widenbauer and Kruger (972) believe they have shown that this synthesis does take place but that none of the vitamin is absorbed from the large intestine. The higher thiamine content of cow's milk may be a result of this synthesis in the cow's rumen.

Lawrence and co-workers (461) recorded 35 to 40 mcg. of total thiamine per 100 ml. of cow's milk and others (528) have reported 27 to 71 mcg., with a mean of 42 mcg. per 100 ml. Sugar added to a formula will increase the thiamine requirement. Knott (436) found the average thiamine content of various formulas of pasteurized milk boiled for 3 minutes to be 24 mcg. per 100 ml. of milk. Boiling for 3 minutes caused a loss of 8 per cent of the thiamine. The range of thiamine for pasteurized and boiled milks was between 18 and 35 mcg. per 100 ml. Evaporated milks had a slightly lower range, 13 to 27 mcg. of thiamine, averaging 19.

Beriberi in breast-fed infants was first described by Hirota in 1898 (361). Andrews (20) in 1912 succeeded in producing experimental beriberi in puppies that were allowed to suckle upon mothers whose own offspring had just died of beriberi. In 1916 Segawa (755) reported nervous symptoms in a breast-fed infant, which vanished quickly when the mother ceased to feed her baby and reappeared when the milk of the mother again was used. He did not realize that this was beriberi. Inaba (392) in 1917 suggested that these nervous symptoms might be infantile beriberi, and, in 1922, Toyoda (907) claimed that the cause of this breast milk intoxication was the same as that inducing infantile beriberi. The 1928 report of the committee on beriberi in the Philippines indicated 16,500 infant deaths annually from this disease, a number which represented 28.1 per cent of the total infant deaths in that territory (921). According to Ching-Lang (126) the symptoms of beriberi develop on the third or fourth day of life and consist of cyanosis, dyspnea, and sometimes cardiac enlargement. If not diagnosed, the condition ends fatally. In a case described by Mata (546), the Filipino mother had no severe symptoms of beriberi, merely some edema and diminished deep tendon reflexes; nevertheless the symptoms in the infant were marked.

Clements (133) reported a condition of partial thiamine deficiency in 8 per cent of 150 breast-fed infants receiving milk containing about 5.0 mcg. per 100 ml. He described the three symptoms characteristic of the condition as: failure to gain in weight at a normal rate, constipation, and vomiting which disappeared upon the administration of thiamine either to the mother or to the infant.

Haridas (338), in 1947, described beriberi in 139 Singapore infants of whom 123 were breast-fed and 14 fed condensed or evaporated milk. The youngest infant was 7 days old. In the breast-fed group the symptoms occurred usually between 1 and 4 months of age and consisted of listlessness, limpness of the limbs, breathlessness, slight edema, and absence of knee and ankle jerks. The most common postmortem finding was enlargement of the heart, particularly of the right ventricle. The heart was sometimes as large as that of a normal 10-year-old child. Ohta (643), in a series of 430 cases of infantile beriberi, found 96.3 per cent of the infants were breast-fed. In the Philippine Islands where infantile beriberi is frequent Albert (12) found 4 cases of congenital beriberi among 514 beriberic infants.

The first case of congenital beriberi reported in the United States was described by Van Gelder and Darby (921) in 1944. A Louisiana mother had limited her diet to apples, bananas, grapefruit, grapes, tomatoes, raw turnips, six slices of white bread, and one glass of milk daily. The mother had mild edema of her face and extremities during the last 3 months of pregancy, with normal blood pressure and urine. The infant became cyanotic immediately after birth and subsequently had repeated cyanotic attacks requiring the administration of oxygen. Retraction of head and convulsive movements developed 30 hours after birth. Forty-two, 50 and 62 hours after birth, 50 mg. of thiamine hydrochloride were administered intravenously with dramatic improvement and final recovery.

The breast milk of beriberic mothers, besides being deficient in thiamine, contains toxic factors such as glyoxal, which explains the violent symptoms in acute congenital or infantile beriberi (250, 821).

A deficiency of the mother during pregnancy may be of importance to the infant,

particularly if breast-fed. When the tissues at birth are not saturated, symptoms of thiamine shortage may develop earlier than in infants born of well-fed mothers. Hamil and co-workers (331) found the average maximum excretion of thiamine in the urine of newborn infants was 13 mcg. per 100 ml., dropping in breast-fed infants during the first week after birth to zero on the seventh day, indicating the very low thiamine content of breast milk and the low storage in the newborn. Williams and associates (981), however, are of the opinion that the human body is capable of storing considerable quantities of thiamine. Slater and Rial (783) also believe that a storage in the infant at birth is used during the first few months until the diet supplies sufficient amounts of the vitamin. Pratt *et al.* (687) found 187 to 382 mcg. of thiamine in the placentae from nine healthy women.

In Norway during the war the thiamine content of the breast milk of some women was less than 3 mcg. per 100 ml. (903). Many breast-fed infants were very constipated and vomiting was frequent in some, but weight gains were satisfactory. It is possible that constipation and vomiting may be symptoms of low thiamine intake even if other clinical symptoms are not noted.

RIBOFLAVIN

Riboflavin is widely distributed in animal and plant tissue and is probably present in all cells in the human body, taking part in a series of enzyme systems associated with the intermediate metabolism of food, particularly carbohydrates. It is a constituent of several known enzymes, either as riboflavin phosphate or as riboflavin adenine dinucleotide, and is found in food both in free and chemically-bound forms, the latter occurring for the most part in vegetables. The best sources of the vitamin are milk, yeast, and meat, especially liver. The minimum daily requirement for an infant is 500 mcg. according to the United States Food and Drug Administration. The National Research Council recommends an intake of 600 mcg. per day for the middle part of the first year of life.

Since 1938 when Sebrell and Butler (754) were able to produce experimental ariboflavinosis in women, numerous investigators have reported cures of the typical syndrome with pure riboflavin. However, Warkany and Schraffenberger attracted attention by reporting malformations in young born of female rats fed a riboflavin-deficient diet. Previously, Coward and Morgan (150) had shown that a lack of riboflavin in the diet of rats may result in cessation of oestrus but the cycle could be restored by giving riboflavin unless the deficiency had lasted about 10 weeks, when the damage became permanent. Warkany and Schraffenberger (948) found that mature female rats on a diet lacking riboflavin, when bred to stock males, gave birth to normal offspring if they conceived immediately. If, however, conception was delayed, the young were often resorbed or the rats often became sterile before pregnancy took place. Between normal fertility and sterility, however, there seemed to be a stage in which defective offspring developed.

Warkany and Nelson (942) had reported in 1940 that female rats reared and bred on a diet consisting of yellow corn meal, wheat gluten, calcium carbonate, sodium chloride, and viosterol gave birth to young, one-third of which had congenital skeletal malformations. On this diet the females were retarded in growth and maturation,

but when they were finally bred many became pregnant and delivered young at term, some of which could be recognized as abnormal by external inspection. The malformations consisted in shortening of the mandible, tibia, fibula, radius, fingers and toes, and in cleft palate. Great variations were noticed in the degrees of the abnormalities. Histologic examinations showed that not only osseous but also cartilaginous structures were deformed, demonstrating that faulty ossification was secondary to abnormalities in earlier stages of skeletal development (944, 945, 949).

Further experiments (948) showed that the preventive factor was riboflavin. A lack of this factor was found to interfere with the normal chondrification which begins in the rat on the fourteenth and fifteenth days of prenatal life (949). According to Warkany (949) a critical stage exists at the thirteenth or fourteenth rat embryo day in which the presence or absence of sufficient riboflavin decisively influences the development of the embryo. Previous to differentiation of membranous skeletal elements, undifferentiated mesenchymal structures exist. This change from mesenchymal into membranous skeleton seems to be impaired by deficiency of riboflavin (949).

In these experiments a low level of riboflavin affected only some skeletal structures adversely, while others were spared. The deformities seemed to take place in the transverse plane of the body. Skeletal parts near the mid-dorsal line were often normal while the ventrodistal ones more often were deformed. The most natural explanation seemed to be that in a borderline deficiency there might be enough riboflavin for the early development of the membranous skeleton, the proximal, and first differentiated structures, but not amounts sufficient for later development (949).

In man, malformations until recently have been considered results of changes in the "germ plasm," genetically determined and hereditary in origin. Dunn (210), however, points out that developmental processes can be altered by environmental disturbances in the same way as by abnormal genes. The first deviation noted may be reduction of growth, to which the different parts of the embryo respond in different degrees as determined by their normal speeds of development. The type of abnormality is thus determined by the normal pattern of differentiation at the time growth is retarded. Dunn believes that harelip, cleft palate, some cases of vertebral fusion, and a number of other abnormalities in human beings belong in this category.

Snyder (802) called attention to an assumption that the genes, or certain surface areas of the genes, act as enzymes or catalysts, absorbing specific protoplasmic substances in definite proportions and causing interactions between them. Riboflavin is an essential constituent of a number of important enzyme systems performing specific functions in the body. Warkany (949) and Dunn (210) suggest that a nutritional riboflavin deficiency and a defective gene may lead to the same congenital abnormality because the same enzyme system necessary for the normal development of the skeleton is disturbed. Environmental changes brought forth by nutritional experiments may thus contribute to the understanding of gene actions and not conflict with the results of genetic and nutritional investigations into the causes of malformations. Snyder's statement (802) that normal development of an embryo must depend both upon a normal environment and a normal make-up of genes may refer, not to a gap, but rather to a combination of factors in the very first developmental

stage of the embryo. This knowledge previously has been of rather theoretical significance. Since the work of Hale (326) and of Warkany and co-workers, it has become of practical importance. We know from biochemical and pathological studies that numerous nutritional disturbances may occur in pregnant women. The discovery of critical periods in the development of the embryo, in which there is unusual susceptibility to nutritional deficiency, emphasizes the importance of prenatal and even prematernal nutrition.

There are few reports of recognized riboflavin deficiencies during pregnancy in the literature. In 1945, Braun and co-workers (78) found, among 900 pregnant women of poor economic status from Jerusalem, 190 presenting various symptoms of riboflavin deficiency, the most common being glossitis and heartburn. Often these symptoms were accompanied by cheilosis, angular stomatitis, and corneal vascularization which appeared usually during the last trimester of pregnancy, with regression shortly after delivery. The diets of these women had consisted principally of vegetables, fruits, and carbohydrates and provided an average daily intake of less than 1.3 mg. of riboflavin. The average riboflavin excretion in the urine was 95 mcg. per liter, compared with 360 mcg. per liter in a control group of normal pregnant women. Of 33 patients treated with 5 to 15 mg. of riboflavin orally for 3 to 7 days, striking effects were shown by 31. The treatment not only eliminated the local symptoms but was followed by improvement in the general condition of the woman. The authors stressed that gestation evidently was a precipitating factor because symptoms were not manifest before pregnancy, and the syndrome occurred frequently in successive pregnancies, affecting only the pregnant mother and not the other members of the family, with cessation after delivery or death of the fetus *in utero*. Heartburn is so common during pregnancy, even with normal stomach acidity, that in such cases a riboflavin deficiency might be suspected. Violent heartburn also may stop instantaneously at delivery and not return.

In a recent study by the same authors (91) 325 pregnant women were divided into 4 groups according to their riboflavin excretion in urine (Table 17). A relationship was found between low riboflavin excretion in the urine and prematurity, vomiting, antenatal death of the fetus, hypogalactia, and agalactia.

Deficiencies of riboflavin during pregnancy may be caused by an incomplete intake, but there are various conditions in the mother organism which under increased demand may produce a shortage, such as slight metabolic disturbances or changes in the absorption mechanism. We know also that vitamin inhibitors (993) exist, substances which have chemical structures similar to the vitamin and apparently displace the vitamin from its normal physiologic role. Woolley (992) and Kuhn and co-workers (451) have produced riboflavin deficiency in bacteria with a riboflavin analogue in which the methyl group is replaced by chlorine atoms or the pyrimidine ring of the riboflavin is replaced by a benzene ring. Such "phenazene" compounds were shown to produce riboflavin deficiency in bacteria and mice, and vitamin inhibitors may be of importance in relation to riboflavin just as salicylate is an inhibitor of vitamin K.

There are very few data pertaining to congenital storage of riboflavin in the fetus. Hamil and co-workers (331) found an average riboflavin excretion in the urine of

newborn infants of 140 mcg. per 100 ml. the first day of life, decreasing during the first week to 2 mcg. on the seventh day. The large amount excreted directly after birth apparently represented tissue storage during intrauterine development. Whether this store is extracellular, intracellular, or attached to some particular organ, is not known. From analyses of tissues from human adults, large amounts, 16 mcg. per gram, are found in the liver, and 20 to 25 mcg. per gram in the kidney (856). Placentae from healthy women (687) averaged 151 mcg. per 100 gm. of fresh tissue. Human blood contains about 50 mcg. per 100 ml. (831) and the urinary riboflavin excretion of normal adults has been found to range from 320 to 1250 mcg. per day (231, 831, 839).

The quantity of riboflavin in human milk varies with the intake of the mother. According to Doxiades (199), Muller (609), and Neuweiler (626) about 25 per cent of riboflavin ingested appears rapidly in the milk. According to Neuweiler (626) human milk contains from 16 to 52 mcg. per 100 ml. The average riboflavin content of human milk as given by Jeans and Marriott (409) was 40 mcg. for each 100 ml.

TABLE 17

COMPLICATIONS OF PREGNANCY AND RIBOFLAVIN EXCRETION IN URINE (91)

Riboflavin (gm. per liter)	Group A: 0–100		Group B: 100–200		Group C: 200–300		Group D: 300	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Total cases	60		62		123		81	
Toxemia of pregnancy	1	1.6	1	1.6	7	5.7	6	7.4
Vomiting and nausea	20	33.3	15	24.2	8	6.5	5	6.4
Prematurity	10	16.4	8	12.7	7	5.7	4	4.8
Hypogalactia	20	33.3	15	24.2	7	5.7	5	6.2
Agalactia	4	6.6	2	3.2				
Antenatal death of fetus	3	5.0	3	4.8				

From analyses of 333 samples of mature milk collected from 80 women throughout 10 months of lactation, Roderuck and co-workers (713) found the average value for total riboflavin in mature human milk to be 41.3 mcg. per 100 ml. for women on diets planned by a dietitian, and 35.4 mcg. for women on self-chosen diets. Free riboflavin was found to compose from 43 to 86 per cent of the total riboflavin in mature milk. Macy (528) found values in the literature ranging from 13 to 100 mcg. per 100 ml., with an average of 47 mcg. Roderuck and co-workers (715) reported secretion in mother's milk from a riboflavin intake averaging 3.1 mg. daily. The mean riboflavin content increased with milk production from 10 to 490 mcg. daily. In mature milk 3 to 15 per cent of the intakes were secreted. The excretion in the urine ranged from 12 to 82 per cent of intake.

Cow's milk contains more than 3 times as much riboflavin as human milk. Normal market milk contains (461) 200 mcg. of total riboflavin per 100 ml., depending somewhat on the breed of cows and on the season of the year. From a survey of the literature, Macy *et al.* (528) found values for riboflavin in cow's milk ranging from 20 to 342 mcg. per 100 ml. and averaging 158 mcg. A few hours' exposure of milk in clear

bottles to direct sunlight causes loss of as much as one-half of the riboflavin, but there seems to be no loss during pasteurization. Riboflavin in milk seems to be stable during sterilization (938) and during the preparation of evaporated (760), dried (182), and homogenized milk (870).

NIACIN

Niacin, or nicotinic acid amide, like thiamine and riboflavin, is a compound of oxidation-reduction enzymes of the body playing a vital role in all biological oxidation. Niacin is present in the tissues as the coenzyme and is present in all living cells. The concentration is fairly uniform but highest amounts have been found in the liver, the kidney, and the muscles (135). The concentration of niacin in the blood of adults ranges from 0.30 to 0.83 mg. per 100 ml., with the greater part in the corpuscles (240, 438, 568, 659, 693). Niacin and some of its metabolites, nicotinuric acid, trigonelline, and *n*-methylnicotinamide, are excreted in the urine. The quantity excreted and the relationship among these substances seems to depend upon the amount and form of the niacin in the diet (135). If excess tryptophan is ingested, niacin need is known to be less.

The dietary allowance of niacin recommended for women by the Food and Nutrition Board is 11 to 15 mg., varying according to their activity, and 18 mg. during pregnancy. Values for the actual requirement of niacin during pregnancy are not available. Siddall (777) pointed out that the highest incidence of pellagra in the southeastern one-quarter of the United States is among adult married women, which suggests a relationship between pellagra and pregnancy. Oldham and co-workers (644) found the niacin excretion in young women fairly constant, averaging 1.0 mg., regardless of levels of niacin intake. The excretion in feces is approximately the same in amount as urinary excretion and rather constant. We do not know if this holds true for pregnant women, nor are there reports of specific niacin deficiency during pregnancy.

Lwoff and co-workers (499) found that the human fetus has no reserve of niacin, and all the fetal organs except the heart have a lower content than the corresponding organs of the mother. Their work indicates that the human fetus has an insignificant store of this nutrient and if its requirement is not secured by biosynthesis in its own intestine, as suggested for various of the B complex factors, the infant from birth must depend on food for niacin (223). However, Hamil and co-workers (331) found greater amounts of nicotinic acid in the urine of infants during the first 3 days postpartum than the usual levels in urine from adults. Pratt *et al.* (687) found in 9 placentae as little as 7.6 mg. and as much as 17.4 mg. of niacin, with an average of 2.0 mg. per 100 gm. of fresh tissue.

Lwoff and co-workers (498) considered the normal level of niacin in blood to be 70 mg. per 100 ml. and, in 15 of 21 pregnant women, found a mean niacin content of 57 mg. per 100 ml. The mothers' principal complaint was fatigue. In two instances the niacin concentration in the cord blood was greater than in the mother's blood prior to delivery.

Lwoff and collaborators (498) found the niacin content of human milk (500, 501, 502), to be 50 to 90 mcg. per 100 ml. from the second to the ninth day of lactation, increasing to 150 to 340 mcg. per 100 ml. between the ninth and sixteenth days post-

partum. In colostrum they found 0.16 mg. per 100 ml. Injection of 1 gm. of nicotinamide caused a rise within 2 hours in the nicotinamide content of the milk, especially when the content was low.

Williams and collaborators (982) in 9 samples of human milk collected from 5 subjects found 120 to 220 mcg. of niacin per 100 ml., with a mean value of 160 mcg. Macy (527) recorded a mean of 75 mcg. in 29 samples of colostrum collected 1 to 5 days postpartum, and 60 to 360 mcg. per 100 ml. in the secretion after the fifth day. The mean secretion of niacin in 268 samples of mature milk was 183 mcg. per 100 ml.

In the literature, Macy *et al.* (528) found values for niacin in cow's milk ranging from 19 to 150 mcg. per 100 ml., with an average of 85 mcg. Lawrence and co-workers (461) found no loss of nicotinic acid in cow's milk exposed in a milk bottle to direct sunlight for 2 hours, nor from pasteurization or storage in the frozen state at about −14° C. for 2 months. Hodson (365) found that irradiated, evaporated, and dried milks on reconstitution have as much nicotinic acid as fresh whole milk.

The actual requirement of niacin in infancy is not yet known, but the majority of infants thrive on amounts of 1 to 11.5 mg. according to the estimated value contained in human and cow's milk. The recommendation of the Food and Nutrition Board for niacin during infancy is 4 mg. daily. The intakes from food by both breast-fed and artificially fed babies are far less than this amount.

On the basis of the diet of middle-class people in England during the Second World War, determined by Kodicek (439) to be between 8 and 12 mcg., Clements (135) estimated that an infant about one year old would have a maximum intake of about 3.1 mg. daily. During the war Clements (135) assumed there had been no niacin deficiency evidenced from this amount nor from a presumably lower intake.

The disease known as pellagra is probably the result of multiple deficiencies. Niacin is certainly a prime factor in the etiology of the disease, but it appears that other factors must also be considered, without knowing what these factors are. According to Eddy and Dalldorf (216) the first report of pellagra in infants was given by Strambio in 1794. Dodd (195) states that infantile pellagra has been described in infants 2 months old. As far as we know, congenital pellagra has not been reported. Most of the cases described in the literature (135) were breast-fed and in nearly all infants the mothers had the disease. Spies and co-workers (809) examined 200 pellagrins in the Nutrition Clinic, Birmingham, Alabama, of whom 6 were infants and 194 were children. They state that a careful history of the mother often revealed that her diet during pregnancy and lactation was inadequate and that as a result the quality of her breast milk was poor. The nursing infants, therefore, had to be weaned soon after birth.

All authors seem to agree that pellagra during the first year of life is rare and occurs only in infants born of pellagrous mothers. Trowell (909) reports 26 children suffering from pellagra, and 4 of these were approximately 1 year old. The infants were irritable and restless. Of the clinical symptoms, edema and skin lesions were found, with changes in hair (alopecia), nails which cracked easily, aphthous stomatitis, and microcytic and macrocytic forms of anemia. Diarrhea was always present. Pathological examinations demonstrated remarkable atrophy of the thymus gland. Later

Trowell (910) found recovery with nicotinic acid in only 3 of 7 cases, probably because the infants presented symptoms of multiple deficiency.

Diarrhea is common in infancy. The response of some infants to administration of nicotinic acid or yeast may be dramatic (809). The diarrhea in an 11-month-old infant, after persisting for months, ceased within 24 hours after administration of nicotinic acid (809). Similar improvement also follows the administration of monocarboxylic and dicarboxylic acids of pyrazine (57, 809).

Cases are described in the literature (463, 730) showing that overdoses of thiamine and ascorbic acid may precipitate symptoms of pellagra in "subclinical" cases of niacin deficiency. Attention has been called to the fact that sulpha drugs and penicillin may act as inhibitors and produce niacin deficiency with lowering of the urinary niacin output (223, 224, 225, 337). Ellinger and Shattock (225) described the production of "black tongue" after oral administration of penicillin, evidently the first case of canine nicotinamide deficiency occurring in a human being. The authors consider the oral administration as the possible cause of the tongue being part of the symptom complex. All these publications point to the fact that vitamins, as involved in the whole metabolism of the cells as the B complex factors are, also are influenced by coexistent factors. We do not know what symptoms express a human nicotinic acid deficiency. Dann (172) believes that the determination of adult requirements, or the factors affecting those requirements, cannot be accomplished before more valid methods of diagnosing human nicotinic acid deficiency have become available.

FOLIC ACID

Folic acid (pteroylglutamic acid, vitamin B_c, vitamin M) is isolated from liver, from yeast, and from leafy vegetables and seems to be necessary for hematopoiesis in animals and human beings. It is necessary for the growth of certain bacteria such as *Lactobacillus casei*. In chickens this factor prevents anemia and it has been found effective with certain macrocytic hyperchromic anemias in man. In celiac disease, folic acid has been found of value in treating the concurrent anemia.

The requirement of this factor in infancy is not known. Williams and co-workers (982) found in mature human milk 45 mcg. per 100 ml. but Macy *et al.* (528) found only 0.22 mcg. The same authors reported 5 and 0.29 mcg., respectively, per 100 ml. of cow's milk.

Zuelzer and Ogden (1005, 1006, 1007) stated that the so-called "megaloblastic anemia," which they found common in white infants, is a result of folic acid deficiency. The characteristics of the circulating blood are a normochromic and usually macrocytic anemia, leukopenia, neutropenia, and thrombopenia. This syndrome is the result of a specific dysplasia and dysfunction of the bone marrow, developing in the absence of an essential hemopoietic principle. It can be recognized by characteristic morphologic changes in the marrow cells and responds specifically and predictably to folic acid as well as to liver extract. The authors presented cases of 25 white infants, 2 to 16 months old, 4 of whom were prematurely born. In every case folic acid or liver extract had a distinct curative effect. The reticulocytes in the blood began to rise between the third and fourth day and shortly afterwards the hemoglobin level and the red blood count began to improve. The bone marrow underwent a

striking transformation from the megaloblastic type to a normal pattern within a few days. In the fully developed lesion of the marrow both erythropoiesis and leukopoiesis were affected. This marrow pattern indicates a disturbance of regeneration, based on faulty karyokinesis. The large size of the megaloblasts and the abundance of the cytoplasm suggest combining cell growth in the absence of an adequate mechanism for cell division. For the leukocytes the granulopoiesis is comparable to that in erythropoiesis. Both lead to a decrease in the number of mature cells, that is, to anemia and leukopenia, because of reduction in mitotic activity at normally the most active levels of multiplication. The infants were socioeconomically at the average for the community or better. In 6 of 23 mothers in the group whose blood was studied, anemia existed when the patients were seen or had existed during pregnancy. The mothers of the 2 exclusively breast-fed infants had conditions associated with achlorhydria, which suggests a deficiency in the composition of the breast milk. In all cases the recovery resulting from folic acid or liver therapy was permanent; thus the disease seems to be different from pernicious anemia in adult life, when combined treatment is necessary.

Davis (183) believes that the mechanism of this action of folic acid or liver extract in the treatment of anemia is to increase the cholinesterase activity in the body. He has produced hyperchromic anemia in dogs by the subcutaneous injection of 3 mg. of acetylcholine twice daily and in other dogs by oral administration of 200 mg. of choline chloride twice daily. Acetylcholine-like activity (13 mcg. per cent) was present in the serum of anemic dogs at one and one-half hours after the ingestion of 200 mg. of choline chloride, but was diminished during treatment with folic acid or liver injection. Serum cholinesterase activity observed in one dog during anemia was increased about 12-fold during treatment with liver. The incubation of blood sera from dogs or men with liver extract or with folic acid increased its cholinesterase activities. The authors also found that serum cholinesterase activity was increased in two human subjects by the ingestion of 5 and 7.5 mg. of folic acid.

According to Krehl and co-workers (449) there seems to be a close relationship between niacin and folic acid, for addition of folic acid to the diet of niacin-deficient dogs makes them able to maintain a more adequate blood picture.

IRON

Hugounenq (386), Brubacher (88), and Camerer and Söldner (112) analyzed human fetuses of various ages and found that the iron transport from mother to fetus is about 0.4 mg. daily in the first two-thirds of pregnancy. For the last trimester, iron transfer may average 4.7 mg. per day. If the adult requirement is 12 mg. per day (257, 764), the fetal requirement forms 39 per cent of an adult's daily need during the last 3 months of pregnancy.

The report of the White House Conference on Child Health and Protection (967) gave a calculated value of 189 mg. for fetal iron content at birth and an average of various analyses of mature human fetuses showing a total iron content of 375 mg. Macy and Hunscher (525) found an accumulation of 246 mg. of iron at term, 0.009 per cent of the birth weight. The iron content of an adult (967) is about 4.5 gm., 0.007 per cent of body weight.

The iron content of the infant at birth seems to depend upon the maternal intake during pregnancy. Pommerenke and co-workers (671), by studying the effect of radioactive iron given to women just before delivery, found that the iron reached the fetal circulation within 40 minutes after ingestion, which pointed to the fact that iron was distributed through the plasma rather than the blood cells. The maternal organism must provide this storage principally during the last 3 months of gestation, and has additional needs for iron in hypertrophic muscles, other tissues, and in the placental circulation. Smythe and Miller (797) showed that the iron content of adult rats just after giving birth was considerably lower than that of females which had not reproduced. Kojima (441) made similar observations on the amount of iron in the different organs of the pregnant rat: only the uterus was higher in iron than that of non-pregnant females.

Coons (141) was first to study iron metabolism during gestation and, in 1932, reported 23 iron balances for American women at different stages of pregnancy. With intakes varying from 9.69 to 19.45 mg. of iron per day, the retentions varied from 0.88 to 6.97 mg., except for one negative balance of 2.21 mg. The author concluded that 13 of the balances showed retentions below fetal needs, indicating that some of the requirement of the fetus was secured from the maternal organism. In 1935, balances were determined for 15 Norwegian women (896) in the thirtieth to thirty-ninth week of pregnancy, whose iron intakes were 6 to 28 mg. daily. For 13 of these balance studies the retentions were below the daily fetal need. The lowest daily intake giving a positive balance was 13.3 mg. A negative balance occurred, however, on an intake of 15 mg. daily. The form in which iron is chemically bound in different foods seems of great importance. Inorganically bound iron is better absorbed than that organically bound, making choice of foods important. Further, the hydrochloric acid present in the stomach is a deciding factor in ionization, and thus in absorption.

Hypochromic anemia has been found so frequently in pregnancy that it has been considered a physiological condition mainly attributable to hydremia. Nalle (615) recorded an anemia in the third month with progression to the seventh. Of 200 women living in good surroundings, 22 per cent showed blood counts below 3.5 million. Bland and associates (62) found anemia in 62 of 100 private patients. Strauss and Castle (824, 827, 828, 829) showed that anemia during pregnancy is frequent, partly as result of low iron intake and partly owing to lowered acidity in the stomach, and thereby reduced ionization of iron resulting in lowered absorption. In 1935, Toverud (896) found that approximately one-fourth of 200 Norwegian women were suffering from anemia during the last 3 months of pregnancy.

Fullerton (268) concluded that anemia due to iron deficiency is frequent in women of the poor classes in Aberdeen and that the diets of poor women are very frequently inadequate for the iron demands of menstruation and pregnancy. The period of pregnancy and lactation combined (406 days) he calculated to represent a daily iron loss of just 2 mg., equal to the iron loss during a correspondingly long menstruation period. The fact that retentions of 2 mg. per day were not found in these Aberdeen women studied provides an explanation for the anemia found in most women of

certain age groups, whether pregnant or not. Davidson *et al.* (178) found in Edinburgh a progressive fall in hemoglobin level during the course of pregnancy, most marked in women who had had three or more pregnancies. Figures for 1944 were approximately 10 per cent higher than those for 1942, possibly owing to the introduction of national wheat meal flour.

The greatest part of the body iron is concentrated in the blood at birth, since at that time the hemoglobin content ranges from 15 to 25 gm. with a mean of 22 gm. per 100 ml. of blood, owing to the low oxygen tension of the placental circulation. After the lungs begin to function, less hemoglobin is needed, and the excess is extracted and stored in the liver. This process continues for the first 9 to 12 weeks of life until hemoglobin values reach their minimum, 10 to 12 gm. per 100 ml. Then the values rise to 11.5 to 14 gm. per 100 ml. at the age of 5 months and remain there for the first year of life if the iron intake is adequate.

The chief source of iron in early infancy is the excess hemoglobin in the blood. Until the period of hemoglobin breakdown is passed the infant is storing iron from this source. Then, Stearns and McKinley (817) found, he must draw on the amount stored in the liver, for the daily intake from either human milk or cow's milk will not supply his needs. At this time the hemoglobin may drop unless iron or iron-containing foods are added to the diet.

The iron present in the body is contained in the hemoglobin of the red blood cells and as a fixed constituent of tissue (814). Hahn (325) described the different forms in which this element may occur in tissues. Spectrographically, Fox and Ramage (263) showed that iron in some form is present in all cells of the body. The iron in the hemoglobin of the red blood cells under normal conditions constitutes about 55 per cent of the body iron. Other important fractions are found as the non-circulating compound in the striated muscles (10 per cent) and as the so-called parenchymal iron (1 to 3 mg. per 100 gm. of fresh tissue, or 15 per cent). This last fraction is considered as functional iron of the tissues. Finally, 20 per cent is left in some form as "available storage" for body needs, such as the production of new hemoglobin. The chief depots for the storage of iron are the liver, spleen, bone marrow, and, under some conditions, the kidneys. These tissues vary widely in their capacity for storage, which in the normal animal is dependent on the previous diet (67).

Iob and Swanson (399) found the increase of iron with age of the fetus due to loss of water during development rather than to an actual increase in the amount stored in the body. Although the hemoglobin level of the blood of premature infants at birth is approximately the same as that of full-term infants, their smaller sizes and storage capacities, coupled with their more rapid growth from birth, would make these infants more likely to develop anemia than full-term infants.

Bunge (93, 94, 95), in 1889 to 1892, was first to call attention to the importance of the congenital store of iron. Various French publications in the first decade of this century described the "chlorotic anemia of infancy," which Marfan (532), in 1906, noticed was sometimes congenital and was present in the first few days of life. Cautley (118) stated in 1910 that the essential cause of common anemias during infancy was a primary iron deficiency in the fetal tissues. This was supported by the analyses of

Ashby (26), who found that the percentage of iron in the liver dropped steadily from 0.058 per cent at birth to 0.013 per cent at 7 months, which was approximately the percentage found in 2 normal adult livers of persons dying as the result of an accident.

In the years following, German pediatricians headed by Czerny (159) frequently talked about a toxic factor in milk causing infantile anemia. Lichtenstein (480) and Lande (455), however, pointed to the low iron store in the premature infant as an explanation of the marked anemia common in these infants. Lande suggested that the greater the prematurity, the smaller the iron store. The studies of Mackay and co-workers (516) in London showed clearly that a deficiency of iron in the infant was the determining factor and that the congenital iron storage was important: the lower the birth weight of the infant, the greater the possibility of anemia. They also found that infants born of mothers anemic during pregnancy had lower hemoglobin percentages in the blood throughout the first 6 months of life than infants born of non-anemic mothers.

The total iron contents of the livers of mature newborn infants were determined by Gladstone (286) in 1932 to be about 32 mg., exclusive of iron as hemoglobin, but information regarding the diets of the mothers was not given. Ramage and co-workers (696) corroborated the findings of Bunge. Strauss (823), who previously had studied anemia during pregnancy, made the suggestion that the common form of anemia during infancy was due to a deficient storage of iron in the fetus resulting from deficient maternal supply. Davidson and Leitch (177) showed that this supply may be depleted through generations.

The livers from 100 stillborn infants, of whom 47 were full-term and 53 premature, were analyzed by Toverud (895). While the average non-hemoglobin iron was 45 mg. per 100 gm. of tissue in the full-term infants, the average was 38 mg. for the premature infants, with the lowest amounts in the most premature. When the iron content of the liver of premature infants (7 cases) approximated the average for full-term infants, the diet and health of the mothers during pregnancy had been very good. The iron content of the full-term infants' livers varied considerably and was lowest for the infants born of anemic mothers and those whose general health during pregnancy had been poor.

Public health efforts have shown that anemia during pregnancy and during infancy can be prevented by supervision, with regulation of the diet and addition of iron when hemoglobin declines. Coons (141) considered the iron requirement during pregnancy to be 15 to 20 mg. per day. McCance *et al.* (503) and Macy and Hunscher (525) concluded that 20 mg. was a satisfactory daily iron intake. Serum iron or hemoglobin percentage should be determined regularly throughout pregnancy, and attention directed to gastric acidity. The incidence of premature births is lowered by raising the general health of the mother during pregnancy and the number of newborn infants with low iron stores is reduced.

The iron content of human milk (528) varies from 1.5 to 4.5 mg. per liter, averaging 2.1 mg. Fullerton (268) estimated that a woman loses about 1 mg. of iron per day in milk. Records showing changes in the iron content of the breast milk dependent upon the iron content of the diet have not been published. The recommendation by the Food and Nutrition Board (257) of 15 mg. of iron daily for a lactating woman

should provide for a loss of about 1 mg. of iron per day. Cow's milk contains 0.1 to 10.0 mg. of iron per liter, with a mean value of 1.3 mg. (528).

The copper content of human milk (528) ranges from 0.4 to 0.6 mg. per liter, averaging 0.4 mg. For cow's milk the range is 0.03 to 4.0 mg. per liter, with a mean of 0.3 mg. The higher copper content of human milk may be a factor in the better blood formation in breast-fed compared with artificially fed infants.

Whether so-called "physiological" anemia in the second or third month of life is physiological or may be prevented by supplementing the milk feeding with iron is not clear (814). As cow's milk is a poorer source of this mineral than human milk, this question is of greater importance for artificially fed infants. Stearns (814) states: "Opinion as to the effect of iron feeding on the rate and duration of blood destruction varies. Evidence has been presented that prophylactic feeding of small amounts of iron shortens the period of physiological hemoglobin breakdown in premature infants and permits a level equal to that maintained by healthy full-term infants." Smith (790) says "there is reason to doubt that the physiological anemia can be prevented by increasing dietary or medical iron early in the anemic period. Nothing seems to be gained by beginning the ingestion of extra iron very soon after birth, except the comfort that it will be available when in the course of his development the infant finds himself able to convert some of it into hemoglobin."

At about 4 months it is wise to add iron-containing foods to the diet. One microgram of iron per kilogram of body weight, daily, appears to be sufficient for the well infant. Few natural foods in the amounts which an infant can ingest at that period in life can supply more than 1 mg. of iron daily. Some pediatricians, particularly in Europe, have considered harmful the addition of green vegetables or other iron-containing food to the diet at the age of 3 or 4 months. Experience shows, however, that infants tolerate such additions very well. As early as 1923 Brenneman (80) pointed out that infants did better when finely sieved or mashed vegetables were given early in infancy. Caldwell (108), for a series of 60 infants fed strained vegetables between the ages of 6 weeks and 9 months, reported that all but a few thrived. Poole and associates (676) gave 215 infants vegetable soup from the ages of 2 to 8 weeks and purees at the fourth and fifth months and found higher hemoglobin values than in a control group. Since 1939 about 5000 Norwegian babies have been given vegetable puree from 4 months of age with excellent results.

The studies of Mackay and co-workers (516) showed that the congenital iron store and the iron deficiency diet common in infancy were deciding factors in development of alimentary anemia. Guest and Brown (321) found this nutritional anemia characterized by microcytosis and hypochromia of the red cells and that iron therapy produced a rapid increase in the mean size of the cells as well as in the hemoglobin concentration per cell. In a later publication Guest and co-workers (322) found hemoglobin below 10 gm. per 100 ml. most frequently at the age of 1 to 3 months when the red cell counts also tended to fall to lowest levels. Later in infancy (8 months to $2\frac{1}{2}$ years) the size and hemoglobin content of the red cells decreased.

It is evident that an infant who has been ill or who is susceptible to colds will retain iron poorly and become anemic. The addition of 5 to 10 mg. of iron as a ferrous or ferric salt seems adequate to prevent such anemia. It is also evident that the baby

born prematurely is usually smaller and contains less blood than the average full-term infant and therefore has less excess hemoglobin to break down and smaller amounts of iron to be stored for future use. Further, prematurely born babies are expected to grow at a rate sufficiently rapid to permit them to equal the size of full term babies at a relatively early age, thus increasing the possibility that they may become anemic earlier than infants born at term unless additional iron is given.

As the congenital store of iron and the iron supply from hemoglobin are unknown, it is wise with any small, weak, or premature infant to consider the addition of iron salts early. Theoretically, ferrous salts are preferable, but in the small amounts given ferric salts are probably reduced in the gastrointestinal tract to ferrous salts, for both seem equally well utilized. Overdosage with iron salts leads to gastrointestinal distress and, through the precipitation of iron phosphate in the intestine, may lead to rickets. At the health center of Oslo, all premature infants have been given additional iron from 1 month of age throughout infancy, and alimentary anemia has disappeared except when current disease has interfered with absorption and utilization of the iron.

VITAMIN K

Vitamin K counteracts both the lowering of prothrombin common during infants' first 6 days of life without other symptoms of deficiency and the lowering found in infants suffering from hemorrhagic diathesis with bleeding from various parts of the body. After the first week of life, in which digestion is established, vitamin K is formed in the intestine by bacterial action.

Chemically, vitamin K is 2-methyl-3-phytyl-1,4-naphthoquinone and is less active than various other anti-hemorrhagic compounds based on chick assays and expressed in 2-methyl-1,4-naphthoquinone units per milligram and per micromol. The following tabulation shows the effectiveness of the various compounds with vitamin K activity (14):

	units per milligram	*units per micromol*
2-methyl-1,4-naphthoquinone	1000	172
2-methyl-1,4-napthohydroquinone	930	162
2-methyl-1,4-napthohydroquinone diacetate	450	116
2-methyl-1-4-amino-1-naphthol hydrochloride	470	99
2-methyl-1,4-naphthohydroquinone-diphosphoric acid	490	260
2-methyl-3-phytyl-1,4-naphthoquinone (vitamin K_1)		
Natural	300	136
Natural, dihydro diacetate	100	54
Synthetic	290	131
2-methyl-3(?)1,4-naphthoquinone (vitamin K_2)	240	139

Vitamin K materials are fat-soluble and depend for their absorption upon the presence of bile salts in the gastrointestinal tract. The richest natural sources of the vitamin are green, leafy foods such as spinach, cabbage, kale, cauliflower, nettle, and chestnut leaves (14). Requirements for vitamin K are not known.

Some newborn infants show a tendency to bleed spontaneously from various mucous membranes. Watts (952), in 1752, was probably first to describe an umbilical

hemorrhage. About 100 years later, Rillich (706) commented on intestinal hemorrhage in newborn infants, and 2 years later Bowditch (72) noticed that there was an association of intestinal hemorrhage and umbilical hemorrhage. In 1852, Minot (586) observed 46 cases of hemorrhage from the umbilicus in newborn infants, pointed to its frequency, and noted that a diathesis was present in these infants. In the same year Coale (136) reported the symptom complex which is now considered hemorrhagic disease of the newborn.

Little (482), in 1861, was first to call attention to the relationship of what was called asphyxia neonatorum following difficult and instrumental deliveries to mental and physical defects that later developed into mental deficiencies and spastic states. In 1890, Kundrat (452) described cerebral hemorrhages as accidental findings in necropsies of Vienna infants several weeks of age. In many of these brains he found blood pigment and signs of old hemorrhage. Townsend (906) noted in 1894 the frequency of a tendency to bleed in newborn infants and reported that in 10,700 cases 50 infants were found to have multiple hemorrhagic lesions. He stated that the umbilical bleeding which previously had received so much attention was a part of a general hemorrhagic tendency and was first to call the condition: "Hemorrhagic Disease of the Newborn."

Ten years later, Coburn (137), seeking the reason for poor vision in infants whose eyes did not show appreciable changes, found peculiar retinal pigmentation, diminution in the size of the retinal vessels, pallor of the disc, feeble pupillary reflex phenomenon with pupils sometimes large and with uncertain or nystagmic movements of the eyes. With the changes appearing at such an early age, it seemed necessary to seek the cause at the very threshold of life—at childbirth or before. Examining newborn infants he found retinal hemorrhage present in 46 per cent. Previously, retinal hemorrhages had been observed at various European clinics in percentages varying from 10 to 40. Coburn noticed that these hemorrhages at birth occurred most frequently in Negroes, in congenitally weak infants, and in those with hemorrhagic diathesis. Stumpf and van Sicherer (834) also were aware of congenital retinal hemorrhages.

In 1912, Whipple (964) described a case of melena neonatorum in which thrombin was not found in the blood at autopsy. Later (965), he concluded that "melena neonatorum in many, perhaps all, instances is characterized by a relatively sudden disappearance of prothrombin from the blood." This condition, he stated, "develops during the first two weeks of life and is often fatal. The cases react favorably to fresh serum treatment." A few years later, Green (309) called attention to the prolonged clotting time in infants with cerebral hemorrhage, and in 1920 Rodda (709) discussed the topic more thoroughly. At the clinic of the University of Minnesota, postmortem examination revealed cerebral hemorrhage in more than 50 per cent of all infants that died intra-partum or during the first few days of life, often in non-instrumental or even easy deliveries. It was evident that pathological changes had occurred in the blood of infants with hemorrhagic diathesis, and he found in them prolonged blood clotting times which became normal after transfusions. One year later, Warwick (951), from the same department, reported that bleeding from other organs occurred in infants who died from cerebral hemorrhage.

Freud (265), as early as 1897, expressed the opinion that prematurity was produced

by the factor producing diplegia, and Browne (86) stated that intracranial bleeding was 16 times more frequent in premature than in full-term infants. Raisz (695) found fetal hemorrhage in 23 per cent of premature stillborn infants and in only 5 per cent at term. Yllpö (1000, 1001) found traumatic lesions in 90 per cent of premature infants.

In Dublin, Saunders (736) found a much higher percentage of cerebral hemorrhages, 61 per cent as compared with 1.89 per cent, among premature infants delivered spontaneously than among full-term infants. Ford (258), on the other hand, stated that prematurity was not the important cause of diplegia, because over 50 per cent of his cases were full-term. This would not preclude, however, diplegia being a major factor in prematurity in 50 per cent of the cases.

Rydberg (726), in the autopsy of a Danish infant weighing 2400 gm. who died 1 hour after birth, found considerable softening of the white substance and the cortex of the brain, similar to the findings he described in connection with cerebral hemorrhages, and considered the process prenatal in origin. Patten and Alpers (658) published analyses of 30 infant brains, in 26 of which they found petechial hemorrhages, scattered mainly in the white matter around the ventricles but also present in the cortex. The latter, however, were more difficult to find. The authors concluded that the hemorrhages occurred prenatally and had no relation to trauma.

Freud (265), in 1897, actually stated that all diplegias dating from birth really had their pathological origins long before birth, which is not a factor in their development. Pierson (666) commented that "most of these important developmental defects of the central nervous system are not injuries caused at delivery but are either defects of the germ plasm or the effect of the environment on the growing embryo in the uterus." The deaths of 38.8 per cent of 953 newborn infants sectioned in Norway (897) in the years 1924 to 1933 were attributed to cerebral hemorrhages. In this group (56.2 per cent were prematures) a close relationship was observed between the occurrence of cerebral hemorrhage and poor health of the mother during pregnancy. Pregnancy was normal for only 17 per cent of the mothers whose infants had cerebral hemorrhage. In one-third of the infants spinal hemorrhages also had occurred. Fifty-six of the 370 infants with cerebral hemorrhage were studied thoroughly and in 11 the bleeding definitely was prenatal in origin. By sectioning the jaws to study the calcification of teeth, organized hemorrhages were sometimes found. Giant cells present in such hemorrhagic areas indicated the bleeding had taken place days or weeks before delivery. These findings showed that extensive pathological changes had been occurring in the fetal organism and indicated that such changes may be the predisposing factor for the occurrence of most cerebral or other hemorrhages in the newborn.

Later, Javert (403) also pointed out that hemorrhagic disease of the newborn is influenced by antenatal and internatal factors. With an incidence of 0.77 per cent in the hospital and 0.304 per cent in the out-patient service he stressed the fact that maternal debility antepartum, complications (62.5 per cent), and age of the mother appeared to have an influence. One-third of these babies began to bleed during the first 24 hours after birth; in only 2 cases was the onset of bleeding later than the first week postpartum. The multiplicity of the lesions suggested that the condition

is a generalized systemic process. Bleeding precipitated by vascular trauma probably continues in these infants when the clotting or bleeding mechanism is abnormal. In this series, 2.5 per cent of 439 neonatal deaths were due to hemorrhagic disease. The author believed that the same factors which cause excessive bleeding in the mothers probably predispose the infants to abnormal bleeding. He found that postpartum hemorrhage (600 ml. of blood or more) was 265 per cent more frequent in these deliveries than in others. He found normal clotting time of 4 minutes in 62 of 72 cases; in 10 cases the clotting time was prolonged (average, 27.4 minutes).

Javert (404) reported bleeding *in utero* evidenced by bloody amniotic fluid in 2 cases and intraplacental and retroplacental hematomas in a third case. In the latter, prothrombin concentration in the infant's blood was only 13 per cent of the adult normal level but the concentration in the blood of the mother was normal. The author believed that the low prothrombin concentration in the infant might be the precipitating factor in cases of premature separation of the placenta. Javert pointed to the probable role of labor in producing hemorrhages and of deranged clotting mechanism in permitting these hemorrhages to continue.

The first systematic study of the prothrombin content of the blood of newborn infants was made at the State University of Iowa by Brinkhous and co-workers (81) in 1937. Prothrombin was found to vary from 14 to 39 per cent of the adult level, with lowest values in the first week after birth. In one case of hemorrhagic diathesis a value of only 5 per cent of the adult level was reported. After transfusion, prothrombin rose to 35 per cent and remained there.

Later studies have verified that there is an actual drop in the prothrombin content of the blood during the first weeks of a newborn infant's life (729), an occurrence which was found to be so common that it was given the name "physiological hypoprothrombinemia" by Waddell *et al.* (932, 933), who found blood clotting time of the newborn could be returned to normal by injecting vitamin K 24 hours after birth. These authors emphasize the importance of administration of this vitamin to the mother. That this physiological hypoprothrombinemia was not "physiological" but was dependent on dietary insufficiency was shown by Waddell and Guerry (934). The prothrombin level of newborn infants was found to be much higher in summer than in winter (801), presumably because the summer diet of the mothers contained more green vegetables.

Kark and Lozner (414) reported four cases of malnutrition with prothrombin deficiency owing to insufficient supplies of vitamin K which responded to administration of the vitamin. More recently, Aggeler and associates (8) reported a case of severe anorexia nervosa associated with purpura, with marked hypoprothrombinemia, which responded promptly to vitamin K treatment. Smith and Warner (795) found high prothrombin figures at birth in infants delivered by mothers from rural districts who stayed in the hospital days to weeks before delivery and ingested a good diet while hospitalized.

Studies of the result of the administration of vitamin K to the infant at birth and to the mother just previous to or during labor have shown that such additions raise the prothrombin content of the infant's blood to normal values. Javert and Moore (405) concluded that the prothrombin molecule does not cross the placental mem-

brane. They determined the prothrombin in the blood of 20 parturient women at term and in the cord blood of their infants and found the concentration, expressed in per cent of the adult normal, was 77 for the mother and 23 for the infants. Hellman and Shettles (346) found an average prothrombin level of 102.5 units of "prothrombin dilution" in mothers and 22.2 units in full-term infants. Premature infants showed a mean level of 8.3 units. Addition of vitamin K to the diets of 2 mothers during the last two months of pregnancy resulted in increases in prothrombin levels from 94 and 120 units to 158 and 274 units, respectively, and in levels in their full-term infants' blood of 77 and 83.8 units, respectively. Shettles and associates (766) stated later that the prothrombin level in the newborn infant usually is higher when the vitamin K is given to the mother previous to delivery than when the vitamin is given after birth.

Plum and Dam (669) reported cases of intracranial hemorrhage for which K avitaminosis was thought responsible. Of 17 observations it seemed evident that in 4 of 11 fatalities, lesions could not be incriminated for the bleedings and they considered the hypoprothrombinemia with lack of coagulation to be the cause of death.

For years, retinal hemorrhages have been discussed in relation to hemorrhagic diathesis: Stumpf and van Sicherer found them in 54 per cent of newborn infants (834); Coburn (137) in 46 per cent of newborn infants; McKeown (518) in 42.1 per cent; and Konigstein (442) in only 10 per cent. Pray and co-workers (690) found a definite decrease in these hemorrhages when vitamin K was given to the mother. They divided their subjects into 3 groups: 1 group received vitamin K (menadione) from 6 weeks to 3 days before delivery; another received the vitamin during labor; and mothers in the third group were not given vitamin K. Retinal hemorrhages occurred in 44 per cent of the untreated group, 19 per cent of the group receiving the vitamin from 6 weeks before delivery, and 13 per cent of the group receiving vitamin K prior to labor. As a rule these retinal hemorrhages disappear soon after birth and usually do not damage the light-perceiving cells. In other cases they may persist as scattered degenerated spots and show that bleeding tendency is present.

In Denmark, Wille (977) reported retinal hemorrhage in 42.4 per cent of 594 newborn infants. Among the babies of the mothers who received intramuscular vitamin K at the commencement of labor (10 mg. 2-methyl-1,4-naphthohydroquinone-disuccinate) retinal hemorrhages occurred in 32.9 per cent (152 infants). In infants of mothers who received daily the same amount of the preparation orally during the last days or weeks of pregnancy the incidence of retinal hemorrhages was 29.3 per cent (164 infants). When the same quantity of vitamin K was given at the start of delivery, hemorrhages were found in 48.3 per cent of infants of mothers receiving intramuscular injections (58 infants) and in 40 per cent of those infants whose mothers were given the vitamin orally (65 infants).

While most studies of newborn infants have shown the prothrombin content of newborn infants' blood to be low, the mother's blood has been reported to show no change. Kern (420) determined the prothrombin content of the blood of normal women in the first months of pregnancy and he found it to vary from 103 to 113 per cent of adult level. From the fifth month of parturition it rose to a maximum of 134 per cent. During labor the prothrombin level fell to 116 per cent. In the blood

of the newborn the level was about 60 per cent of that of the adult. A relationship between the maternal and the infant prothrombin levels was not found. According to Kern, variations in maternal prothrombin during pregnancy and the diminished prothrombin in infants are probably due to endogenous factors rather than to variations in the intake of vitamin K. Davidson and Tagnon (175) have taken the normal values in mother's blood as proof that low prothrombin in the infant is not attributable to deficiency in the mother. The storage in the maternal and fetal tissue, however, must be considered in relation to infection, even when the circulating blood does not show changes.

At present the significance of this hemorrhagic tendency at birth is not clear, nor is its relation to lowered prothrombin content, frequent accidental finding of intracranial hemorrhage, to stillbirth, neonatal death, or to the various spastic cerebral palsies and other neurological manifestations seen at different ages in childhood. McGovern and Yannet (514) call attention to the fact that of 67 cases of infantile spastic cerebral palsy with marked mental defect the group of unknown causes represented 54 per cent. Their cases of unknown origin had many features in common with spastic diplegias and the authors suggest that they probably represent prenatal conditions leading to developmental cerebral defects.

It is clear that any condition which involves the integrity of brain cells will threaten the infant's mentality and perhaps his life. In recent years the problem of anoxia in newborn infants has been recognized, especially in relation to birth. Schreiber (742, 743, 744, 745), stressing the effects of excessive amounts of analgesics and anesthetics in connection with labor and delivery, showed that any factor which deprives the brain cells of oxygen may result in various degrees of damage, from slight brain injury to death, whether the inciting factor acts by depressing the respiratory center, by reducing circulation, by reducing the oxygen capacity of the blood, by chemical changes lowering the availability of the oxygen present, or by inhibiting utilization of oxygen from a plentiful supply. The possible association of these factors with nutritional status prenatally and with the problem of hemorrhage in relation to vitamin K and hypoprothrombinemia cannot be disregarded.

In discussing the preventive value of vitamin K, differences in terminology must be recognized. While nearly all investigators agree that prothrombin levels are increased by administration of the vitamin, the effects in terms of reducing cerebral hemorrhages and mortality rate are not established. Since the influence of vitamin K on the prothrombin content of the newborn infant's blood became generally known, obstetricians in various countries have recommended a preventive dose of vitamin K, usually during labor, in part to determine whether the "physiological hypothrombinemia" might be prevented and whether the occurrence of cerebral hemorrhage could be reduced, thereby lowering neonatal mortality (36, 47, 68).

During the first 6 days after birth, Bruchsaler (89) found prothrombin values of from 54.4 to 58.3 per cent of the adult level in infants' blood without treatment, from 59 to 84.4 per cent when the infant was given the vitamin, and from 63.3 to 83 per cent when the mother was given vitamin K during labor. Hellman and Shettles (347) reported neonatal mortality reduced from 4 to 1.5 per cent by prenatal administration of vitamin K to the mothers, but Sanford and co-workers (732) could

not find that vitamin K given by mouth to the infant directly after birth or to mothers before delivery changed the incidence of hemorrhagic manifestations or per cent mortality, nor could Parks and Sweet (654) find any difference in neonatal mortality between treated and untreated groups of mothers.

The results are more confused by publications showing no relationship between prothrombin content of the blood and occurrence of hemorrhagic disease. Parmelee (655) reported 2 cases of severe melena associated with marked prolongation of prothrombin time, in which the bleeding did not stop following vitamin K administration although prothrombin time returned to normal promptly. Scobbie (752) reported prothrombin times as prolonged in infants without hemorrhage as those in infants with hemorrhage. Poncher and Kato (674), Kove and Siegel (444), and Snelling and Nelson (800) point to the fact that additional factors may be necessary for a prolonged prothrombin time to produce hemorrhage. Finally, Potter (681), in a study of 6560 and 6630 pregnancies in 2 successive periods in two years, with and without vitamin K to the mother before and during labor, found no significant differences between fetal and infant mortality rates in the 2 groups.

One of the first experimental studies showing occurrence of both intracranial hemorrhage and hemorrhage in other parts of the body was made by Moore and co-workers (594) with rats fed a diet containing: casein, 18 per cent; hydrogenated cottonseed oil, 3; cod liver oil, 2; salt mixture, 4; dextrin, 71; and, yeast, 2 per cent. Seventy-three per cent of the young showed various nervous symptoms and died shortly after birth. Autopsies disclosed extensive visceral and intracranial hemorrhages. Increasing the yeast in the diet from 2 to 7 per cent decreased mortality of offspring to 9.3 per cent and greatly lessened the incidence of hemorrhage. The dietary deficiency evidently was largely one of thiamine, but probably a deficiency of vitamin K also was involved.

Roderick (710, 711) described the pathology of sweet clover disease with a change in the coagulation time of the blood. Griffith and co-workers (317, 318, 319, 320) then described hemorrhages in the kidneys of rats deficient in choline, and Engel and Salmon (235) found that choline deficiency in growing rats produced hemorrhages in the brain as well as in the kidneys.

Ferraro and Roizin (252) described the changes taking place in the brain and other parts of the bodies of chicks and rats suffering from acute and chronic vitamin K deficiency. The early histological changes in both the white and grey matter of the cerebrum and cerebellum were marked, with diffuse vascular congestion dilatations of the blood vessels resembling small aneurysmal dilatations. Besides diapedesis and perivascular edema, discontinuity of the vessel walls was found, with possible formation of large hemorrhages. In the cortical areas of the brain where hemorrhages or vascular changes were not present, chromatolysis, karyolysis, and neuronophagy were detected. All forms of degenerative changes in brain cells were noted in or near hemorrhagic areas.

Later, the same authors (253) gave a detailed account of the clinical and histological picture produced in chicks and rats by acute and chronic vitamin K deficiency. Low blood prothrombin values were found combined with hemorrhages into all the

organs of the body. Marked changes had occurred in the blood vessel walls, ranging from simple swelling and mild degeneration to complete rupture. Traumatic factors played a definite precipitating role in production of the hemorrhages. Fifteen adult pregnant rats on vitamin K-deficient diets gave birth to young presenting spontaneous hemorrhagic manifestations throughout the body, particularly in regions exposed to mechanical irritation.

Brown and co-workers (84) called attention to the fact that cerebral hemorrhages may occur in infant rats lacking both lard and vitamin K. Most of the young that showed hemorrhages were either born dead or died within the first 24 hours after birth. Interference with coagulation of the blood was discounted as a contributing factor to the hemorrhage because the blood of both mother and infant rats showed normal clotting times. These authors suggested that lard and vitamin K are necessary for the production in the body of a substance which prevents the breakdown of capillary structures.

Thus, recent experimental work is highly corroborative of the findings in human beings that there is not a true relationship between prothrombin level and occurrence of cerebral hemorrhages. The animal experiments show distinctly that vitamin K deficiency, either alone or combined with a lack of a substance in lard, produced marked changes in the vessel walls and in the brain substance. Whether or not this capillary fragility is due to a new substance dependent on the presence of vitamin K and lard is not known.

Recalling the facts about hemorrhage in the newborn makes possible better understanding of the conflicting results obtained with vitamin K administration to mother or infant. Definite tissue lesions involving degenerative cell changes, whether in blood vessels or brain substance, will not clear up within a few hours. When vitamin K is given to the mother during labor or to the infant at or after birth the prothrombin content may be entirely normal but the blood vessels still may be defective and brain cells may be degenerated, resulting in symptoms of bleeding or irritation, or complete lack of irritation because of destruction of the cells. It is evident that neonatal mortality may be unchanged under such conditions. If these conditions are results of a vitamin K deficiency alone, or combined with a choline or lard constituent deficiency as in experimental rats and chicks, this process resulting from the deficiency has gone on for some time in the fetal body, and the trauma during delivery is only the factor which precipitates hemorrhage. Under these conditions the only way to avoid the hemorrhages is to supplement the diet with vitamin K and other factors weeks or months prior to birth, thus eliminating the presence of damaged tissue at the time birth trauma occurs.

Even if we do not know the requirement of a pregnant woman for vitamin K, it is wise to recommend that the pregnant mother eat green leafy vegetables every day throughout pregnancy. In regions where these are not available, synthetic vitamin K may be added, at least during the last month of gestation, to an otherwise ample, well-balanced diet. Of 1531 live infants born between 1939 and 1947 (897) of mothers supervised at the Oslo health center and given vitamin K 3 weeks previous to the delivery, not one instance of symptoms of cerebral hemorrhage oc-

curred. The infants and children were observed at the center 9 times during the first year and 4 times yearly till 7 years of age. These mothers also received 45 gm. of brewer's yeast in addition to a good diet.

Vitamin K is assumed to be formed in the intestine by bacterial action but various drugs now in common use influence the supply of vitamin K in the body. Sulfa drugs inhibit the production of vitamin K by the intestinal flora and a pregnant mother given such medication should receive supplemental amounts of this vitamin. Storage of vitamin K is believed to be very limited, and therefore any interference with the normal production must be compensated.

Link and co-workers (481) have shown that when salicylates are given with a vitamin K deficient diet rats develop hypoproteinemia. These workers also found that when the toxic substance in sweet clover disease, dicumarol, which produces hemorrhagic tendency, was used *in vitro*, salicylic acid was formed and that vitamin K was completely effective in preventing the salicylate hypoprothrombinemia in animals. Shapira and co-workers (759), Meyer and Howard (578), and Rapoport and co-workers (698) have demonstrated hypoprothrombinemia in man from administration of salicylate without restricting vitamin K in the diet.

VITAMIN E

In 1922, the existence of an anti-sterility vitamin was demonstrated in 3 laboratories by experiments in which normal female rats ate diets containing all the vitamins known at that time, yet failed to reproduce. The factor Evans and Bishop (242) designated as vitamin E occurs in lettuce, wheat germ, cotton seed, rice germ, and a variety of other vegetable oils, but only traces have been found in animal products. Chemically, vitamin E activity is shown by alpha, beta, and gamma tocopherols.

The requirements are alleged to differ for each person and tend to increase during pregnancy, presumably as the placenta grows. According to Shute (769, 770, 771, 772, 773, 774, 775, 776) there is a seasonal change in the requirements and a change with the cyclical phenomena of women. Currie (158) believes 5 mg. of tocopherol to be a safe amount for securing invariable fertility in a 200 gm. rat. If the need for vitamin E is proportional to body weight, a woman weighing 50 kg. would require 1.25 gm., or 10 mg. per day for 18 weeks. Some, doubtless, is available from body stores and food sources, so a therapeutic dose of 6 mg. should approximate the requirements. There is some confusion concerning administration, possibly owing to the difference between 3 minims of oil and a 3 minim capsule of a concentrate prepared from 5 gm. of oil. Abderhalden (3) recommends 20 to 30 mg. during pregnancy.

During the last few years methods of determining the tocopherol content of the blood have been described, permitting deeper insight into the value of this factor. Emmerie and Engel (232) found an average value of 0.438 mg. per 100 ml. of tocopherol in the blood of European adults. In the United States, Wechsler and co-workers (956) found higher levels: an average of 0.96 per 100 ml., with a range from 0.59 to 1.62 mg. After oral administration of tocopherol a rise in the blood content was noticed. Meunier and Venit (577) found much lower values in France, ranging from 0.30 to 0.60 mg. per 100 ml. During the German occupation, values as low as

0.19 to 0.22 mg. per 100 ml. were found in normal men and non-pregnant women, respectively. Low figures also were found during the occupation in Holland (149). The figures of Kofler (440) from Switzerland, ranging from 0.40 to 1.40 mg. per 100 ml. for adults, correspond with the American figures.

The level of tocopherol in the blood does not seem to drop during normal pregnancy; in fact, figures for some pregnant mothers seemed to be higher than those for non-pregnant women, which Varangot and associates (923) interpreted as characteristic and physiologic for pregnancy *per se*. Aberhalden (3) disagrees with the conclusion. Both authors consider the higher tocopherol content of pregnant women's blood a result of better diet of pregnant women during the war and of purely nutritional character.

Abderhalden (3) found a distinct lowering in the tocopherol content of the blood in women living in hotels as compared with those living in their own homes. When diets became very poor after the capitulation in Germany the values became low, necessitating cessation of the determinations. He found that tocopherol in the blood of women having had abortions was sometimes low, sometimes normal. In 6 of 17 women with such histories, blood tocopherol was below 0.40 mg. per 100 ml., and in 1 was 0.16 mg. In such cases Abderhalden added tocopherol to the diet and usually saw a living, normal infant. In the woman showing 0.16 mg. per 100 ml. during the second month of pregnancy, the vitamin E content rose to 0.35 mg. in the eighth month and the infant was born one month prematurely.

The vitamin E content of the blood at various stages in pregnancy has been reported. Rauramo (699), from Finland, found 0.6 to 1.0 mg. per 100 ml. from the sixth to the tenth month of gestation and 0.8 to 1.3 mg. per 100 ml. at delivery, in contrast to values in non-pregnant women of 0.3 to 0.7 mg. per 100 ml. Straumfjord and Quaife (822) also reported increased serum tocopherol in pregnant mothers when large amounts of vitamin E were added to their diets, in some to values 65 per cent higher than those for non-pregnant women. In these women with a high vitamin E intake the placenta and uterus were found to contain considerable tocopherol.

Varangot (922) reported values at the beginning of pregnancy of 1.25 mg. per 100 ml. which rose throughout pregnancy to 1.82 mg. at term and then rapidly fell after delivery. After several months of German occupation, Varangot and co-workers (923) reported that the average values for pregnant women were:

0.34 mg. per 100 ml. in 1–4th month of gestation	(20 women)
0.32 mg. per 100 ml. in 4–7th month of gestation	(22 women)
0.31 mg. per 100 ml. in 7–term of gestation	(32 women)
0.23 mg. per 100 ml., 10 days after delivery	(20 women)

These authors commented on the higher values, during the occupation period, in pregnant than in non-pregnant women and adult men, 0.22 and 0.19 mg., respectively, and questioned whether this was due to mobilization of maternal reserves or to synthesis of vitamin E by the mother or the fetus. They called attention to the fact that the placenta and the anterior hypophysis are the organs rich in vitamin E.

Abderhalden (2) found the tocopherol content of maternal blood to be 0.62 mg. per 100 ml. in German mothers and that of cord blood only 0.10 mg. per 100 ml.

The variations in the cord blood from different infants were great, from 0 to 0.34 mg. per 100 ml. In 7 of 20 cases tocopherol was not detected in cord blood and in 3 cases only faint traces were found. Abderhalden considers the lack of knowledge of tocopherol content of the blood of pregnant women to be responsible for the rather confusing results of vitamin E treatment in instances of threatened abortions reported in the literature.

Vitamin E seems to be distributed between mother and infant in the same way as are vitamins A and K. The blood of the fetus or newborn infant is considerably lower in these factors than that of the mother, which has been considered a sign that the placenta acts as a barrier and transfers only small amounts (890). Evans and Burr (244), however, found the placenta and the anterior lobe of the hypophysis to have the highest vitamin E content. Mason and Bryan (542) found that the vitamin E content of the mother's diet during gestation had an influence on the resistance of the animal to symptoms of tocopherol deficiency postnatally, even if the blood did not show a high content at birth. The newborn from high-vitamin-E rats contained about 5 times the amount of vitamin E found in stock rats. This demonstrates the ability of rats to store the vitamin during fetal life, either in the liver or other parts of the body.

From Evans and Bishop's first publication (242) of studies on rats it is evident that the factor later called vitamin E has a close relationship to the reproductive cycle. When rats were fed casein, corn starch, and lard to which butterfat, salts, and dried whole yeast were added, the rats were sterile. The ova were fertilized and implanted. The placentas, however, showed beginning blood extravasations which increased in extent. Resorption invariably overtook the products of conception. By administration of fresh green leaves of lettuce a sudden restoration of fertility to these animals occurred. The fertility also was restored by adding butterfat up to the amount of 24 per cent of the diet by weight. Wheat germ had the same effect on fertility.

Later studies have verified these findings and it has been found that in the male, vitamin E deficiency produces an irreversible sterility characterized by degeneration of the germinal epithelium. In the female with moderate deficiency, gestation may start normally after conception and may go to term but the young may be born dead or die during the lactation period. In more severe deficiency the fetuses may begin to develop normally but about the middle of the gestation period they degenerate, as does the placental tissue and site of implantation. Finally, the fetus and placenta are resorbed completely. On completion of resorption, normal oestrus starts and the rat is again able to conceive. This so-called "resorption sterility" can be cured by giving a suitable dose of vitamin E at any time before a critical period in pregnancy.

For women with histories of repeated or "habitual" abortion vitamin E has been found beneficial by some authors. Other authors, however, have found no benefit from even high doses of vitamin E given over a long period of time. Good results with vitamin E treatment have been obtained by Vogt-Möller (927, 928), Weinzierl (957), Lubin and Waltman (490), and Ingram (396). Shute (769, 770, 771, 772, 773, 774, 775, 776) has tried to explain this beneficial effect but his results have not been

verified by others. Goodall (296) described the frequency of a general hemorrhagic tendency in pregnant mothers as a cause of their abortions. Hertig and Edmonds (351) reported that in nearly 50 per cent of all spontaneous abortions in women they found deficiencies in the vascular bed and thus lack of circulation.

From the earliest experiments on vitamin E-deficient rats it was generally accepted that the fetus succumbed to starvation and asphyxiation secondary to retarded development and rarefaction. When, however, previously sterile rats were given borderline doses of vitamin E, Mason (540) was able to study various developmental stages, from early resorption to viable fetus *in utero*. Such studies revealed abnormalities of the vascular system associated with later fetal death, consisting of dilatation and congestion in superficial blood vessels. In the capillary bed there often were petechiae-like areas of variable size and shape, which under high magnification appeared to represent localized areas of extensive capillary dilatation and stasis. Fetuses in which death had recently occurred showed striking and irregular distribution of superficial vessels, associated with marked dilatation of deeper vessels in the immediate vicinity. These changes were almost universally accompanied by prominent areas of hemorrhage in the lateral wall and floor of the cerebral ventricles. Histological examination revealed extensive extravasation of blood in the substance of the corpus striatum and adjacent regions of the cerebral hemispheres. Similar lesions were encountered in other regions of the brain and in various tissues such as the liver. The terminal stages of fetal life were characterized by more diffuse areas of hemorrhage in the superficial tissues of the head and body wall, with large areas of superficial edema. The amniotic fluid was usually blood-tinged. Yet such fetuses might be viable. Mason emphasized that these changes are unquestionably pathognomonic for vitamin E deficiency. Their incidence and that of late fetal death have proved to be inversely proportional to the magnitude of borderline levels of graded dosage in bio-assays of the various natural and synthetic forms of vitamin E. Vitamin C and vitamin K added to the diets did not influence the vascular injuries. Blood clotting time was not altered and the vitamin C content of the blood was normal. Dam and Glavind (162) concluded that the ultimate cause of fetal death in vitamin E-deficient fetuses was diminution of the circulatory blood to a level inadequate for continued survival of fetal tissues. Observations of Mason (539) on several thousand human fetuses corroborated these findings.

In 1931, Pappenheimer and Goettsch (651) called attention to definite lesions found in the brains of chicks suffering from a deficiency of vitamin E. The lesions consisted in edema, necrosis, hemorrhage, and hyaline thrombi found in the capillaries in and about degenerated areas. Before death the chicks presented various symptoms of ataxia, tremors, and clonic spasms.

Urner (918) found a tendency to hemorrhage in the placenta of pregnant rats suffering from vitamin E deficiency, and on the tenth day of gestation the pregnant uterus showed a softening; blood was found in the amniotic fluid and the embryo was dead by the seventeenth or eighteenth day of gestation.

In 1943, Patrick and Morgan (657) pointed to the presence of an unidentified, fat-soluble nutrient in yeast and in soybean which seemed to be necessary for the utilization of alpha tocopherol by the chick. Whether this factor is of any significance in human beings has not been established.

Mature human milk contains 0.11 to 1.14 mg. of vitamin E per 100 ml. with a mean of 0.66 mg. (528). Colostrum contains about double the amount in mature milk. Bennholdt-Thomsen and Gaedke (50, 269) have found that administration of vitamin E to lactating women had no influence on milk flow or on the composition of milk. According to Mason and Bryan (538, 539, 540, 542, 543) on a vitamin E-deficient diet male rats born of mothers receiving a diet high in vitamin E showed testicular degenerations in approximately the same length of time as those born of mothers given a stock diet. The male offspring of mothers given a stock diet during pregnancy and a diet high in vitamin E during the first 2 weeks of lactation showed the same degenerative changes, but they occurred after much longer periods of ingesting the E-deficient diet. Thus, "placental transmission of vitamin E in the rat is exceedingly limited, and . . . the vitamin is much more readily transferred through the mammary gland to the milk (543)."

Vitamin E was found important also to the muscle tissue of young growing animals. A deficiency resulted in flaccid paralysis which seemed to be cured by the ingestion of the vitamin (244, 290, 530, 650). As the muscle tissue presented the same appearance as in pseudohypertrophic, muscular dystrophy, it was thought that this disease might be a symptom of such a deficiency. This thesis was found to be invalid, as vitamin E therapy in muscular dystrophy has been without effect on the paralytic state.

Barrie (41) reported symptoms of toxemia in experimental rats as a result of the absorption of dead fetuses and fatty infiltration of the liver. In 1939, Dam and Glavind (162) corroborated the findings of Pappenheimer and Goettsch (651) to some degree. On a vitamin E-deficient diet containing 22 per cent lard, but only protein food which had been extracted with alcohol, encephalomalacic foci developed, combined with an exudative diathesis. Both symptoms could be counteracted by the addition of alpha tocophercol or its acetate compound to the diet. Besides the encephalomalacic lesions, the chicks developed a symptom complex which he named alimentary exudation diathesis. The chicks accumulated fluid in the subcutaneous connective tissue or under the skin, a condition which could be entirely prevented by the addition of alpha tocopherol. Dam and Glavind, therefore, were of the opinion that vitamin E is necessary to the maintenance of normal permeability of capillaries. Since these symptoms appeared rather suddenly in the chicks, the authors believed that the edema was formed from a hypersensitivity reaction which occurred in the chicks in the absence of vitamin E.

IODINE

Since antiquity, pregnancy has been recognized as a period in life when goiter frequently develops. Primitive races for centuries knew the value of seafood products in maintaining the fertility of their women. Among Indians, dried fish eggs and, by some, dried kelp, was used "so that they would not get big necks like the whites (692)." Tait (851) as early as 1875 noticed a step-like enlargement of the thyroid gland associated with consecutive pregnancies. Slight hypertrophy of the gland during pregnancy, often to clinical detectability, is looked upon by many obstetricians as normal even in non-goiterous districts.

The immediate cause of any thyroid enlargement is a relative or an absolute deficiency of iodine. The thyroid is the most vascular structure in the body and is a very labile tissue, capable of marked and rapid hyperplasia and involution in response to variations in functional demand. In animals, when the iodine store falls below 0.1 per cent (349, 466) hyperplasia is initiated, with hypertrophy as a result, which continues until exhaustion or recovery intervenes. Anatomical recovery is involution to the colloidal, or resting, stage and not necessarily the disappearance of the enlargement. Animal experiments (534) have shown that colloidal goiter is the nearest condition to normal that a thyroid gland which has once been in the state of active hyperplasia can assume. Such colloidal glands are capable of manifesting all of the reactions of a normal gland. It is possible to repeat the cycle of hyperplasia, hypertrophy, and involution many times during the life of an experimental animal. The fetal thyroid gland is directly affected by maternal thyroid insufficiency.

Eugster (239), among 898 Swiss children less than 5 years old, found 555 whose mothers were afflicted with goiter; 25.6 per cent of the children also had goiters. Of the other 343 children only 2.6 per cent had goiter. Thus, if a mother has a goiter the possibility of her child having one is ten times as great. Eugster also found that the younger children of a family are more subject to goiter than their older brothers and sisters. His investigations showed that goiter and cretinism run parallel. In Swiss areas free from goiter he did not find a case of cretinism, nor among newcomers to an endemic area. In places with a goiter incidence of 45 to 55 per cent, cretins were found to comprise 0.6 per cent of the population. In villages where more than 55 per cent of the people had endemic goiter about 1 per cent were cretins. In one canton of Berne the goiter incidence was 56 per cent; cretins composed 3.5 per cent. The adult form in all cases was a struma nodosa and the mother of every cretin had a goiter.

Areas free from goiter were found never to produce cretins. Observations of cretin twins showed that there was no hereditary predisposition to cretinism. The constitution, however, was important in determining the type of cretinism, corresponding to the sensibility of the various organs. The development of endemic goiter also depended on surroundings and not on heredity. Greenwald (314), in 1946, concluded that endemic goiter is not due to a lack of iodine, but many data prove that goiter results from depletion of an important nutritional factor necessary for the normal function of the thyroid gland.

Iodine deficiency in the mother results in hypothyroidism in the infant. The weight of the thyroid gland in the normal newborn infant is 1.5 to 2.5 gm. Larger thyroids are evidence of iodine deficiency. The iodine content of cord blood is lower than that of the mother's blood. In a recent report on the pathogenosis of endemic goiter, McClendon and Foster (508) observed the effect of an iodine-free diet on rats under conditions in which exposure to a hypothetical goiter-producing agent might be excluded. After 73 days the rats had thyroid glands weighing about 40 gm. per 100 gm. of body weight, in contrast to 10 gm. for rats given water containing iodine.

The prevention of simple goiter in man was not attempted on a practical basis

until 1917, when Marine and Kimball (533, 535) administered sodium iodide distributed throughout 2 weeks in the winter and spring for a period of 2½ years, to school girls between the 5th and 12th grades in Ohio. Of 2190 pupils, only 5 developed thyroid enlargement, while of 2305 girls who did not receive the prophylaxis, 495 developed thyroid enlargement. Numerous papers have confirmed these results. In 1923, the Swiss Goiter Commission (138) recommended the introduction of state-wide prophylactic measures against endemic goiter, consisting of the use of salt containing 2 to 5 gm. of potassium iodide per kilogram, or administration in the schools, at weekly intervals, of tablets containing 1 mg. of iodine.

In 1924, Marine (533) believed that 2 to 5 mg. of potassium iodide per kilogram of salt would be ample in districts where endemic goiter was not very prevalent. In a period of physiological growth such as pregnancy, however, he thought this amount too small and recommended that all pregnant women living in goiter districts should be given the equivalent of 10 mg. of iodine each week during pregnancy and lactation. Caution must be observed, for the maximum storage capacity of the normal thyroid is not over 25 mg. of iodine.

The etiology of iodine deficiency was clarified by a program of goiter prevention instituted in Michigan and Ohio in 1924 (426), using iodized salt containing 1 part potassium iodide to 5,000 parts of salt. In 1924, the incidence of goiter throughout Michigan was 38.6 per cent, whereas in 1928 it was 9.9 per cent, and in 1935, 8.2 per cent. A study of Houghton County, Michigan, showed that the discontinuance of iodized salt was followed by a marked increase in the incidence of goiter within 3 years.

In 1944, the Goiter Subcommittee of the Medical Research Council of England (551) strongly urged that to all common salt consumed in England one part of potassium iodide be added to each 100,000 parts of salt, that is, 10 mg. per kilogram. A daily intake of 10 gm. of salt would provide 0.1 mg. of iodine, an amount probably insufficient for the needs during pregnancy.

Wespi (959) stated that palpable thyroid gland was found in 25 per cent of all newborn infants of Zurich. After a program in which 20 mg. of potassium iodide was added to each kilogram of salt used, the number of palpable thyroid glands at birth decreased to 6.8 per cent. Wespi discussed the necessity of this amount of iodine and, though he did not determine the exact preventive dose, proved that the 5 mg. per kilogram commonly used is insufficient during pregnancy in a goiter district. According to Kimball (427) the individual requirement of iodine under all conditions cannot be stated accurately in micrograms, but 1 mg. per day from iodized salt is efficient and entirely safe, from repeated study and rechecking over a period of 20 years in Michigan.

Numerous goitrogenic agents are known, of which some occur in common foods such as those of the cabbage family. The composition of food eaten thus has a bearing on iodine requirement and may be one of the explanations for the variation of this requirement from one person to the other, even in goiter districts. The duration of iodine deficiency prior to pregnancy has a decided influence on the daily requirement.

The importance of preventing iodine insufficiency is far greater than just eliminat-

ing deformities of the neck. The prevention of goiter also means control of those forms of physical and mental degeneracy, such as cretinism and idiocy, which are dependent upon thyroid insufficiency. All people in goiter districts should use iodized salt to assure the daily intake of iodine, 0.15 to 0.3 mg., recommended by the Food and Nutrition Board (1948).

The iodine content of human milk varies from 2 to 15 mcg. per 100 ml. and is easily influenced (814) by the iodine intake of the mother. Cows' milk has been reported to contain 0.4 to 187 mcg. per 100 ml., with a mean of 21 mcg. (528). Cod liver oil is one of the best sources of iodine, containing (American) 3.6 to 15 mcg. per gram.

III

PREMATERNAL, PRENATAL, AND POSTNATAL CARE

PREMATERNAL CARE

Hospitals are being built all over the world to provide better chances of survival for infants whose physical status at birth is inferior, as well as to provide medical care for infants and children stricken by illness. It is certain that the condition of infants at birth and their ability to withstand the hazards of infancy and childhood are the result of hereditary factors, maternal and paternal, and of the effects of all supervening experience, both intra- and extra-uterine. In a concept of maternal nutrition the cumulative influences throughout generations must be recognized, as must the effects of experience during the gestational period upon the product of pregnancy. However, from the public health viewpoint it is practical to consider birth as the starting point in the reproductive cycle of an individual and the entire period of growth and development before maturity as preparatory for parenthood. Thus, the advances being made increasingly in the care of the unborn, of infants, and of children also play an important role in "prematernal" care.

Pediatrics is a Greek work which means "healing the child." We who have followed the development of pediatrics have watched one after another of the afflictions prevailing in childhood disappear from the hospitals. Why? In considerable part because increased understanding of the laws of growth and development has produced expanding recognition of the many nutritional factors required in various amounts and proportions for growth and reproduction of cells in different parts of the animal body.

Knowledge of the necessity of vitamin D for normal mineralization has abolished the severe forms of rickets in civilized countries. The extreme deformities seen during and after the First World War were not seen during World War II in countries where food rationing was established. Florid rickets has practically disappeared. Today, infants are seen with slight deviations from normal mineralization detectable by X-ray examination and possibly by biochemical tests. By such analyses Clements (134), Corner (146), and The British Pediatric Association (82), all in the last few years, report rickets in 30 to 50 per cent of infants studied. Others do not consider such findings to be rickets, merely small deviations in growth which perhaps have little significance (409). Deposition of osteoid instead of normally calcified tissue may show by X-ray as a slight osteoporosis, as transverse lines, as a slight softening of the bone in the form of an early craniotabes, or as a slight bowing of the legs near the end of the first year. Such manifestations usually are seen in heavy, rapidly growing infants. Are they a result of defective mineralization and nutritionally preventable, or merely an expression of rapidly growing bone?

Xerophthalmia has almost disappeared with recognition of the requirement for vitamin A by growing infants and children. Again, we may not be aware of the mildest forms of vitamin A deficiency in infancy.

Frank scurvy is rare owing to prophylactic administration of foods containing ascorbic acid to meet demands of cell oxidation and the normal formation of the intercellular substance. Discussion persists regarding the requirement of this factor

in various forms of infant feeding and in relation to the effects of changes in growth rate. The interrelationship between the amino acids and vitamin C is not fully known.

Cretinism and congenital myxedema also have nearly disappeared as the iodine need and the geographical distribution of the element have become more clearly defined.

Infantile beriberi in its manifest forms, still the cause of 50 per cent of infant mortality in the Philippine Islands, is rarely seen in Europe and the northern United States. The mildest form of infantile beriberi, however, still exists but the symptomatology is obscure. The actual requirement of thiamine at all periods in life is uncertain.

Alimentary anemia in infancy also has declined as the laws governing the synthesis of hemoglobin and formation of new red blood cells have become known. The newer knowledge of the congenital iron store, the necessary iron intakes for hemoglobin formation, and the influence of folic acid on the cleavage of the immature blood cells have clarified our understanding of a possible way of preventing the various forms of infantile anemias.

The gradual eradication of these conditions has not been an accomplishment of pediatrics alone, nor of nutrition alone, but has been the result of many varied approaches to the problem of better health. A similar attack on the multiple aspects of neonatal deaths is needed, and sufficient knowledge is now available to permit real progress. "Neonatal" is used to designate various intervals after birth, but official statistics usually record deaths during the first 30 days after birth as neonatal. Infants dead at birth, "stillborn," have posed many problems. In Europe pulmonary respiration is accepted as the criterion of live birth. If the heart beats but the infant never breathes, it is a "dead birth." In Great Britain, however, beating of the heart after birth is accepted as a sign of life even if breathing does not occur. In the United States the criteria for stillbirth vary from state to state. In many countries, statistics for stillbirth rate are combined with those for neonatal mortality because the etiology is considered to be the same. Recognition that deaths a few days or even weeks after birth may result from causes identical with those producing fetal deaths recorded as stillbirths demonstrates the growing realization of the continuity of new life processes from conception to death, the birth process merely achieving for the young individual changes of environment and method of sustaining life.

The infants who die disappear but the damaged infants remain. In a series of 500 patients seen because of cerebral symptoms, 70 per cent of those whose birth record was available had a history of apnea at birth (742). The depressing effect on the respiratory center of birth analgesia given in greater than pharmacologic doses was directly related to the degree of apnea and in many instances was the causative factor in fetal anoxia with cerebral damage to the infant as a sequel. Possible deficiency states of the fetal cells from a deficit in the supply of some nutritional factor may predispose to this anoxia at birth. We know that a cell already damaged will be more severely injured by an unfavorable influence than will an undamaged cell. It is clear that improving all factors involved in minimizing the anoxic state during delivery will contribute toward lowering the infant mortality and reducing cerebral damage to children.

At the end of the first year the normal child is able to move, if not independently,

to such an extent that closer contact with the surroundings is established. Often the result is an increased incidence of contagious and infectious diseases which influence the nutritional status of the child. Appetite may be diminished, absorption and utilization often are lowered, and rise in body temperature increases the requirement for various food factors. Besides the usual benign respiratory infections contracted from adults or playmates, exanthematic infections are common in this period.

In the preschool years the energy requirement per kilogram of body mass is lower than in infancy and feeding problems often stem also from psychological reasons. The child is observing everything in his surroundings, is absorbed in personal activities, and may not be interested in food. Emotional disturbance from efforts to maintain regular feeding patterns may create in the child a dislike for food in general. Some mothers, fearing that their children may be underfed, provide diets with taste appeal, but containing excessive amounts of sweet, starchy foods which satisfy appetite and depress intakes of more wholesome foods.

The period of 5 to 6 years before school is a very important one in a child's life and much depends upon the parents, for the child's positive or negative attitudes towards everything in his surroundings are dependent on the way he is cared for. Whether the child is helped during feeding hours may greatly influence his nutrition because the whole mechanism of secretion by both external and internal glands is dependent on the emotional balance in the organism. A mother's anxiety may find expression in various ways, quite often producing emotional upsets in both the mother and child. When a child begins to play outdoors in the fresh air, feeding difficulties usually decrease. The companionship of other children may be of great help in these years, for the likes and dislikes often dominant in the second to fourth years are reduced by the observation that other children do not have the same preferences.

School age is considered to be the healthiest and happiest period in life and is the period of lowest mortality. Unbounded energy, outdoor sport activities, and a vivid interest in everything keep children active and create a natural appetite for wholesome food. Everything children see and hear in school impresses them and is remembered, often for life. Thus, the school age is of great importance in the nutrition of an individual, for at that time he may learn the basic facts of nutritional science from practical demonstrations in eating.

When the child reaches 10 to 14 years of age he enters a period of great growth and development, with revolutionary changes in the body metabolism. Maturation of the sex glands is started in this period and initiates the formation of new hormones which have a marked influence on metabolic processes. Nutritional factors are closely related to the production of various hormones in the body.

In animal experiments, Jackson (401) found that caloric restriction which would maintain the animal but not permit increase in weight would halt the development of the ovaries, testes, and secondary sex organs. The ovaries were the most sensitive. Even mild caloric restriction for a longer period of time caused cessation of oestrus cycles in adult female animals and atrophy of the secondary sex organs in the males. Recovery of both sexes was possible if the restriction had not been endured too long. After prolonged undernutrition, even to a mild degree, interference with gonadal function and growth was permanent. Changes were most marked if the diet restriction

occurred during the period of puberty. Similar changes were noted (401) in undernourished children.

The changes described by Jackson in 1925 have been explained by depression of the pituitary gland. Mason and Wolfe (541), in 1930, showed that the pituitary glands of starved female animals had decreased gonadotrophic potency. One year later, Moore and Samuels (593) found that a thiamine-deficient diet caused atrophy of the secondary sex glands in male rats, which was produced by depressed pituitary function. Normal testes and secondary sex organs could be maintained by injection of pituitary gonadotrophic extracts, even though the animal died of the vitamin deficiency. They also found that it was the caloric restriction of the diet and not the vitamin deficiency, *per se*, that produced the changes. Drill and Burrill (200), in 1944, obtained similar findings with female rats, which seem to be even more sensitive to undernutrition.

Guilbert and Goss (323) demonstrated in 1932 that protein was a deciding factor. If the protein content of the diet was less than 7 per cent, oestrus became irregular and finally ceased. Pearson (660) indicated in 1937 that lysine might be the limiting amino acid in maintaining ovarian function.

Samuels (731) claimed that sufficient intakes of both calories and protein are necessary to maintain normal pituitary and gonadotrophic function. If the diet does not provide sufficient calories, the protein of both the food and the tissues is rapidly used for energy and the pituitary gland is not able to obtain sufficient material for synthesis of the protein hormones. He described 2 diabetic girls, 17 and 18 years old, whose diet was severely restricted for 4 to 5 years prior to treatment. Neither menstruated until the diet was restored to normal and then the bleeding was very irregular, with infantile vagina and uterus and no development of mammary glands. One remained a dwarf, although her growth in the years before diet restriction had been entirely normal.

Mulinos and Pomerantz (606) have found that both growth and thyroid and adrenotrophic activity can be disturbed by undernutrition of long duration through changes in the pituitary gland. During adolescence, nutritional requirements are increased not only by more rapid growth and greater activity but also by the imbalance existing during these years in metabolic processes and in rate of development of different organs. Thus, the growth of the skeleton is at times more rapid than that of the organic matrix, a situation which often makes motility of the young awkward and accompanied by many unnecessary movements. In addition to the imbalance in physical development of various parts of the body, the adolescent girl and boy are usually emotionally unstable, which has a bearing on nutritional requirements, food intake, absorption, and utilization.

Nutritional deficiencies render adolescents susceptible to such diseases as tuberculosis, dental caries, and mental disturbances. The increasing frequency of such diseases indicates that nutritional background is less adequate than in previous years. The number of cases of tuberculosis has risen in most countries. The curve for dental caries (905) may be fairly low throughout the school age but show a sudden and often marked turn upward as adolescence starts. Some change may occur in the structure of the tooth in this rapid-growth period, making the tooth less resistant

to the caries-acting agents, whatever they may be. That these changes are of nutritional origin is evidenced by the fact that a regulation of the diet to meet requirements in these years of rapid growth has been found to decrease disposition to caries.

In girls the adolescent period usually comprises the years just preceding pregnancy. The importance of preconceptional stores of various nutritional factors must be recognized. Animal experiments have shown that malformations may be the result of an intermediary stage of nutritional deficiency present in the very first weeks of gestation. Occurrences of deficiency states so early in pregnancy evidently are results of poor nutritional condition previous to pregnancy. In many women nausea and vomiting are the immediate result of the nidation of the ovum into the uterine wall. When nutrition has been poor during adolescence and conception immediately is followed by nausea and vomiting, a deficiency state may result which, if severe or prolonged, may jeopardize the outcome of pregnancy.

PHYSIOLOGIC GROWTH DURING THE MATERNAL REPRODUCTIVE CYCLE

All of the knowledge of nutrition which is accumulating emphasizes that the nutritional state of a body is the result of the entire chain of past experiences involving food intake, the processes of their utilization, and external factors influencing the health of the individual. Thus, nutrition in infancy and childhood is a major factor in nutritional status during adolescence, and the entire period of growth and development is the foundation for a healthy adult body.

In girls, growth during adolescence is more complicated than it is in boys, for initiation of reproductive processes, menstruation, represents an additional demand for physiologic growth which normally continues to menopause except during gestation and for a time postpartum. The demands of pregnancy and lactation for physiologic growth by the maternal body are more intense than those of menstruation.

The demands for physiologic growth upon the body of a woman are demonstrated in the schematic diagram in Figure 7. The blood loss attributable to menstruation and interperiod repair of the uterine mucous membrane corresponds to production of about 50 kg. of body tissue in a 30-year period, that is, a woman who does not have children constructs tissue equivalent to twice her adult body weight in the first 45 years of life. If she bears 6 children and nurses each for 9 months, the physiologic growth demands of pregnancy, lactation, and interim menstrual periods are approximately equivalent to construction of 100 kg. of body mass in the 30-year period, and when 45 years old she has built 3 times her adult body weight.

A woman's body is constructed to give rise to a new generation and during a period of reproduction the physiology of her body functions is somewhat altered. As soon as the ovum is fertilized new hormone production is started, and as the ovum grows and new cells are formed in the primary and secondary sexual organs and other parts of her body, the nutritional requirement of all materials is increased. In addition, the maternal body early in pregnancy must nourish the fetus, which further increases nutritional requirements, as does maturation of the mammary glands preliminary to producing food for the infant. In addition to being supplied with proper food, if the physical environment, attitudes, and social conditions are adjusted

to the mother's needs, a feeling of security and stability is created which is reflected in better utilization of the food eaten.

In many early civilizations pregnant women received special consideration and some native races of today provide special diets not only for their pregnant women but also for all girls for a time before marriage. Price (692) states that even the fathers' diets are supervised before marriage. Evidently such regulations resulted from observation and practical experience. Our present knowledge has demonstrated the importance of nutrition throughout the prematernal period of growth and de-

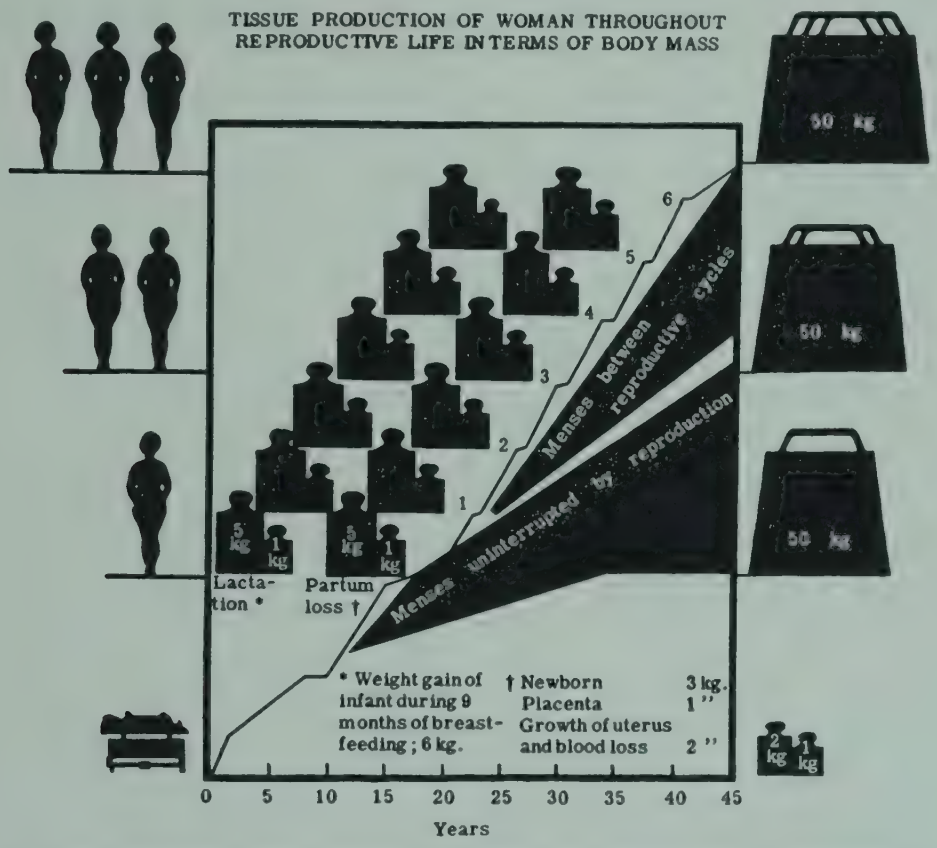

FIG. 7. The physiologic growth required to provide for menstruation uninterrupted by pregnancy between the ages of 15 and 45 years is the equivalent of the woman's adult body mass. If in those years she has 6 children and breast feeds each for 9 months the metabolic demand for tissue production is double her adult body mass.

velopment and has confirmed the need for special supervision of girls during adolescence and women during pregnancy and lactation to assure the best possible nutritional status during these periods of greatest demand for physiologic growth.

PRENATAL CARE

The scientific management of pregnancy designated as prenatal care started in France, where, because of the falling birth rate, interest was directed towards improving infant mortality. The movement was initiated in the maternity hospital in Nancy in 1890, but became associated with the name of Professor Budin, who insti-

tuted in 1892 in the Charité Hôpital in Paris "Consultations Des Nourissons." Care of the expectant mother naturally developed into a department of preventive medicine. Ballantyne of Edinburgh was the pioneer in Scotland. Starting his work at the end of the last century, in his lifetime he saw prenatal care established on a sound basis.

At present some sort of prenatal care is available in most countries, but a visit or two to a clinic, with an occasional examination of the urine for albumin, is often considered sufficient. There is danger that such superficial prenatal care will give rise to a false feeling of security on the part of the supervisor and the supervised. Constant supervision directed toward working out the complete nutritional history and status of the women should be employed to controvert any unfavorable effects of earlier environment and to detect immediately any deviations from normal so that therapy may be started.

Although the importance of prenatal care has been recognized for 150 years, few records are available of systematic care in a population. In a report from the Maternity Center Association started in New York in 1918, Dublin and Corbin (204) in 1930 gave the results with 4726 mothers cared for in 1922 to 1929, of whom 85 per cent had registered before the eighth month of pregnancy. During the 8 years not one woman under care died before delivery, and only 11 mothers died within 1 month postpartum from puerperal causes, a rate of 24 maternal deaths per 10,000 live born infants in contrast to rates in the years 1922 to 1926 of 53 maternal deaths among white women in New York City and 62 per 10,000 for the Bellevue-Yorkville district of the city wherein the center was located. Of the 11 deaths, 4 were due to puerperal sepsis, 3 to hemorrhage, and 4 to embolism and pulmonary conditions. Not one death occurred from eclampsia. The stillbirth rate was 26 per 1,000 births compared with 46 per 1,000 in the city in 1928, and neonatal mortality (first month) was 28.7 compared with 32 for the entire city and 42.9 for the Bellevue-Yorkville district. The authors calculated that the same type of service provided for the whole United States with the same results would have saved 10,000 of the 16,500 mothers who died each year and some 30,000 babies that died annually.

Publications from various obstetrical clinics show that maternal and infant death rates have been lowered extensively in recent years by improved obstetrical skill and better prenatal care. In 1947 the United States had a maternal mortality rate of 13 per 10,000 births (619). Assali and Zacharias (27) reported from Cincinnati a maternal mortality of 17 per 10,000 for the 11 years 1935 to 1945, with the lowest rates, 10 and 13 per 10,000, for the latter years. The major causes of maternal deaths were hemorrhage, infection, toxemia, and heart disease.

In 1945 Howard (381) reported that Connecticut had 10 maternal deaths per 10,000 live births. In 1940 to 1945 there had been 191,747 pregnancies in Connecticut, with 321 puerperal deaths. Deaths from the three main causes were reduced during the 6-year period: for infections, from 11.8 to 2.5; for toxemias, from 7.0 to 2.8; and for hemorrhages, from 8.2 to 4.3 per 10,000 live births. Howard points out that only by constant education of the public and the medical profession in the value of prenatal care is it possible to reduce death rates, and emphasizes the necessity of cooperation among state health departments, hospitals, and physicians.

Gregg (315), in 1942, reported various congenital defects in infants born of mothers who had contracted rubella while in the early part of pregnancy. Of 78 babies having malformations, a history of rubella in the mother was obtained in all but 10 instances, and in these 10 instances, the diagnosis was sufficiently indicated to warrant their inclusion in the group. All of the infants had cataract at birth; 44 had definite congenital heart lesions; 7 were deaf-mutes, and nearly all were under-developed and presented feeding problems. Swan and associates (842, 843) reported that of 49 Australian mothers who had rubella during pregnancy, 31 of the infants exhibited congenital defects of various forms. According to Swan, rubella in mothers during the first 2 months of pregnancy will produce defects in all of the infants, while rubella during the first 3 months causes defective children in one-half of the offspring. In later publications (844, 845) many causes are added. In 1944, Evans (246) reported that dental defects also occur as a result of rubella in the mother during pregnancy. He found retardation in eruption of teeth in 23 of 24 infants whose mothers had rubella during early pregnancy. Later, many reports have contained similar observations on the effects of rubella during early pregnancy (11, 236, 313, 379, 384, 665, 702, 717).

Thus, virus diseases may be important in the development of the fetus when the infection is contracted within the first 6 to 10 weeks of pregnancy and may present many questions of interest, particularly as to whether it is the virus, or the changes resulting from the virus invasion of the organism, which produces malformations. Lynch, who discussed Albaugh's (11) paper, believed that disturbances in the vascular supply of the tissues, rather than the virus itself, cause these gross malformations.

In a recent publication Swan (840) reported 16 instances of maternal rubella among 760 stillbirths in South Australia. In 13 of the 16 women the infection occurred during the first 4 months of pregnancy. Evidently, rubella—by damaging the embryo early in pregnancy—must be considered a possible cause of stillbirths.

Various drugs may influence the fetus. Mosher (605) found that mapharsen, quinine, and sodium salicylate when fed or injected into pregnant animals produced hemorrhages in the labyrinth of the fetus without producing similar hemorrhages in the mother. Taylor (857) has reported an increased incidence of congenital deafness among the offspring of mothers who were heavy users of quinine during the malaria season, probably as an effect of quinine upon the fetal inner ear. Adair and Stieglitz (7), however, observed no harmful effects from quinine. We have many demonstrations that lack of maternal insulin production or thyroid activity causes changes in the corresponding fetal organs and their functioning.

Sontag (803) stated that deep maternal emotion produces increased activity of the fetus, probably as a result of increased adrenalin level in the maternal and, therefore, the fetal blood. Severe maternal fatigue also was found to increase fetal mobility. Various nervous disturbances of the mother promptly affected the fetus. Mothers, for instance, complained of increased fetal activity from the vibration of a washing machine and from various sounds during a concert. Sontag (803) also found that fetuses very active from maternal emotional distress, fatigue, or other causes have low weights at birth and show minimal amounts of fat storage. These various stimuli to the mother may cause disturbances in the autonomic nervous system of

the fetus, followed by postnatal disturbances in infancy such as feeding difficulties in the first month after birth.

Richards and Newberry (704) reported a positive relationship between fetal activity as reported by 12 mothers and performance of Gesell test items by their infants when 6 months old. Obermer (641) demonstrated the increased lability of women during pregnancy by reporting glucose present in 80 per cent of urine specimens passed by pregnant women during bombing periods.

The consequences of non-fatal fetal deprivation of oxygen can become extremely serious in later years. The report in 1938 by Schreiber (742) showed that a high percentage of children seen with neurological symptoms had a history of apnea traceable directly to amounts of anesthetics and analgesics in excess of pharmacologic dosage during childbirth. Preston (691) found that the mothers of 132 children (97 with intelligence from superior to borderline, 35 with subnormal intelligence) needing special pediatric guidance and treatment because of highly apathetic or hyperactive behavioral patterns, or epilepsy, had all been given large amounts of anesthetics and analgesics during childbirth.

Garry and Stiven (270) summarized the literature available in 1935 and concluded that under normal conditions the self-selected diet of the mother had little effect on the weight of the newborn. They pointed out, however, that extreme deprivation by war, famine, or poverty affected both fertility and birth weight, and that the effect of deprivation may be cumulative—affecting the later births rather than the first.

The investigations of Brend in 1917 (79), Murray in 1924 (612), and Campbell in 1929 (114) indicated that there was little or no difference in the average birth weight of children of different social classes in western Europe, although dietary surveys showed that there might be considerable difference in the average food consumption of mothers in different social classes. Abels (4), in 1922, studying the influence of seasonal variations on the nutritional conditions of the newborn in Vienna, found an increase in birth weight during the summer months, more pronounced in multiparas than in primiparas.

Peller (662, 663), in 1923, called attention to the fact that prematurity, and as a result neonatal mortality, was reduced among infants born of mothers who stayed in the hospital one week or more prior to delivery. Woolf and Waterhouse (991) made a thorough study of the influence of social conditions in boroughs of England and Wales and concluded that two-thirds of infant deaths would be avoided in the boroughs by the abolition of conditions defined by their indices. Of the preventable deaths one-third were found to be associated with overcrowding, one-quarter with low paid occupations, one-fifth with unemployment, and one-eighth with industrial employment of women. In England and Wales over 250,000 deaths in 11 years, about 62 per cent of the total deaths, could be attributed to adverse social conditions. Moncrieff (590) published the results of a survey of neonatal mortality from congenital causes among legitimate infants whose parents represented five social classes in England and Wales (Table 18). He found a steep rise for premature birth and congenital debility as the economic level decreases, suggesting that poverty, under-nutrition, and overcrowding are the principal elements in lower income groups which contribute to the poorer statistics. Gerschenson (281) in 1931 stated that the birth weight was

influenced by Russian mothers' nutrition during pregnancy. The following year Balfour and Talpade (35) found an increased average birth weight and a lower incidence of premature births in infants of women in Bombay given a diet containing whole wheat or millet, compared with women whose diet consisted largely of polished rice.

In 1933 a statistical study (885) of 4251 Norwegian infants over a 10-year period (1920–1930) showed definite seasonal variations in birth weight, with a peak in the month of August. Similar results were obtained in a maternity home in which pregnant women received a good diet under controlled conditions (885). The results of the systematic prenatal supervision were shown by an average birth weight of 3587 gm. for the full-term infants of 348 mothers who had resided in the home for 2 months or more before delivery, whereas the average birth weight of full-term infants born of mothers who had stayed 6 weeks or less before delivery was 3347 gm. For full-term infants born of mothers who entered the home after delivery the average weight was

TABLE 18

MORTALITY FROM CONGENITAL CAUSES FOR LEGITIMATE INFANTS BY SOCIAL CLASS OF FATHER, ENGLAND AND WALES, 1930–32 (590)

Social Class	I Professional and well to do	II Intermediate	III Skilled workers	IV Intermediate between skilled and unskilled workers	V Unskilled workers	All
Congenital malnutrition	5.0	5.4	5.6	5.7	5.4	5.5
Congenital debility	1.4	2.2	2.9	3.3	3.8	3.0
Premature birth	10.5	14.4	16.8	18.6	19.6	17.3
Injury at birth	2.3	2.5	2.1	2.0	2.0	2.1
Other causes	2.8	3.0	2.7	2.9	3.0	3.0
Total	22.0	27.5	30.1	32.5	33.8	30.9

only 3240 gm. Of the 124 mothers entering the home after delivery, 15.3 per cent had infants weighing less than 2500 gm. at birth (898).

In 1935, Tompkins (876) supervised about 2000 pregnant women in Philadelphia given "intensive and persistent dietary instruction throughout the prenatal period." The majority also received polyvitamin supplements. The stillbirth rate, 0.25 per cent, and neonatal death rate, 0.30 per cent, were lower than the rates of 1.4 and 2.0 per cent, respectively, for a control group of 3040 births.

In 1941, Ebbs and co-workers (212) published their first report on supplementing the diets of pregnant women in Toronto, Canada. The incidence of miscarriages, stillbirths, and premature births in the women on poor diets was much higher. The incidence of illness in the babies up to the age of 6 months and the number of deaths resulting from these illnesses were many times greater in the poor diet group. Ebbs and co-workers (215) reported no noticeable difference in the birth weights of the infants in the different groups. At 6 months of age, however, the weights of the infants born of mothers who had received supplemented diets were higher than those of infants from the poor diet group. The most striking observation was that all of the 14 babies that were lost came from mothers in the poor diet group.

One year later the report of the People's Health League (397) showed that after provision of supplementary minerals and vitamins to 50 per cent of about 5000 English women, the remainder serving as controls, evidence of toxemia was found in 30 per cent fewer of the women receiving supplements than in the control group, and the incidence of prematurity was decidedly reduced.

A continuous study of the influence of diet during pregnancy upon fetal growth and development has been in progress in the Department of Child Hygiene of the Harvard School of Public Health for many years. A report in 1943 by Burke and co-workers (101) showed a statistically significant relationship between the diet of the mother during pregnancy and the condition of her infant at birth and in the first 2 weeks of life. In the 216 cases studied, all stillborn infants, all infants who died within a few days of birth except one, most infants who had marked congenital defects, all premature, and all functionally immature infants were born to mothers whose diets during pregnancy were inadequate. A relationship was found (99) between the prenatal dietary rating and the course of pregnancy. This relationship, however, was not so marked as that between the prenatal dietary rating and the condition of the infant, indicating that when nutrition during pregnancy is inadequate the fetus suffers to a greater degree than the mother.

Williams and Fralin (980), in 1942, published the results of a survey of the diets of 514 women during pregnancy; the diets of only 10 were good, of 209 were fair, and 295 had a poor diet. The authors did not find a relationship between dietary adequacy and the outcome of pregnancy, but the numbers of stillbirths and neonatal deaths were too small to show any positive relationship to dietary inadequacy.

In a much larger group studied in England by Balfour in 1944 (34), a positive relationship of maternal diet to fetal development and health was found. In 10 areas in the North of England and 19 in South Wales, 11,618 pregnant women received food supplements consisting mainly of vitamins A, D, and B complex, with calcium, phosphorus, and iron. In a control group were 8095 women who did not receive supplements. Both groups were getting extra milk in some form. A significant reduction was found in the stillbirth and neonatal mortality rates of the supplemented diet group. In Glasgow, Cameron and Graham (113) at the Royal Maternity and Women's Hospital found mothers with full-term infants had had diets superior to those of mothers of stillborn and prematurely born infants.

Kerr (423) concluded that increased weight gains in pregnant mothers were associated with increasing weight of infants at birth, but that the latter increase had no influence on the duration of labor.

Studies during the First World War did not provide significant information concerning the effect of food restrictions on maternal and child health. The few observations made were not systematically planned to determine the effect of various dietary deficiencies in pregnant women. Moreover, many vitamins and other nutritional factors were unknown at that time.

From World War II Smith (791) reports that "During the 6 or 7 months which preceded the liberation of northwestern Holland in May, 1945, a state of severe generalized undernutrition was prevalent in urban areas. The effects of this nutritional crisis upon the infant at birth were investigated especially in the cities of Rotterdam

and The Hague. During the period, and apparently because of the low food supply, about 50 per cent of urban women became amenorrheic and presumably infertile. The birth weights of infants decreased, and rose after restoration of food, in a manner indicating that fetal weight gain is particularly related to the maternal diet of the last half or last trimester of pregnancy. Significant decline in birth length also occurred, but was less clearly apparent than the change in weight . . . prematurity was insignificantly increased. Stillbirth was definitely not increased, nor was neonatal mortality among infants born in hospitals. The sharp fall in conception rate associated with amenorrhea resulted in so few pregnancies that data were inconclusive as to the relation between undernutrition in early pregnancy and malformation of the fetus. A slight but statistically insignificant increase in malformation did occur." The explanation, Smith (792) believes, is that the Dutch women had been reasonably well-fed until subjected to a brief period of about six months of acute general undernutrition but the possible effects of starvation upon the male population cannot be disregarded.

Dieckmann *et al.* (193) did not find definite changes in the amounts of various food factors in the blood of pregnant women, nor any clinical evidence supporting the value of mineral salts and vitamins added to their previous diet. However, if the basal diet to which those women were accustomed was sufficient to meet the maternal and the fetal needs, no result could be expected from the additional food intake. The investigators mention that no study in the literature has included a large enough number of subjects to give significance to any changes which occurred. The study of Balfour (34), however, included about 20,000 individuals and produced definite data showing an influence of maternal diet on the fetus and on childbirth. Some criticism has been directed at the accuracy of the various types of diet studies, and the value of studies of the effect of diet upon the fetus and childbirth would be enhanced if prematernal dietary patterns were investigated in relation to parity, age of mother, and length of pregnancy.

Besides nutrition of the mother during pregnancy, other factors influencing women's health in this period may have a bearing on the birth weight and the nutritional status of the newborn infant. According to Hirsch (362) strenuous work during the latter part of pregnancy increases the number of prematurely born infants and infants of low birth weight. He quoted Ferrara, who found that the duration of the mother's rest from outside work before delivery determined to some extent the birth weight of the infant. According to Schneider, also quoted by Hirsch, the number of premature infants increased definitely in Germany during the First World War, when women had to replace men in all kinds of work.

Toverud (885) found the birth weight of full-term infants born of illegitimate mothers living unprotected in the community to be lower than the weight of legitimate infants (Table 19); but unmarried mothers are younger, on the average, than those who are married, and the uncertainty of their lives and the mental pressure under which they live may play a role in the results. It is possible to increase the birth weights of the illegitimate infants of even the youngest mothers by supervised prenatal care within the protected environment of a maternity home, showing that the age of the mother is a minor factor and difficult social conditions are more decisive factors.

One year later, Bivings (60) reported a difference in birth weight of about 60 gm. between averages for 1801 infants from low social level and 955 infants from the best strata of society in Atlanta, Georgia.

LACTATION

The ability of most women to breast-feed their infants has been taken for granted, as well as the inability of others to feed their offspring successfully. With increased knowledge of the physiology of the entire reproductive cycle we have come to understand that the development of the mammary gland also is dependent upon the general health and nutritional state of the mother. Metabolically, the gland is very active. Radioactive sodium given orally was found in human milk 20 minutes later by Pommerenke and Hahn (672).

There is disagreement regarding the oestral development of the mammae, particularly with respect to their duct system. When pregnancy is initiated, there is a sudden development of ducts, lobules, and alveoli from ovarian hormonal influences. During the second half of pregnancy, secretory activity becomes more and more pronounced,

TABLE 19

CORRELATION BETWEEN WEIGHT, PARITY, AND LEGITIMACY (885)

Mothers' status	Full-term infants	Girls				Boys			
		Firstborn		Others		Firstborn		Others	
		Weight	W/L*	Weight	W/L*	Weight	W/L*	Weight	W/L*
		gm.		*gm.*		*gm.*		*gm.*	
Married	4251	3414	67.8	3563	70.7	3488	68.6	3701	72.2
Unmarried	347	3327	66.5	3482	69.2	3487	68.6	3681	71.5

* Weight-length ratio.

increasing the general size of the mammae by dilation of the alveoli and ducts. In some women, extensive areas of the gland may fail to reach maturity. The secretory process has not been clarified fully but it has been considered to be controlled by an anterior pituitary hormone called prolactin, which, however, has not been proved to have a stimulating effect on milk secretion. Recently, Robinson (708) has verified Hertoghe's (352) previous finding that desiccated thyroid has a stimulating effect on the mammary gland.

In the modern woman failure to breast-feed is common. There are few statistics on the duration of breast feeding, and the causes of failure are seldom given. From a report by the English Ministry of Health in 1944, Waller (936) stated that about 80 per cent of babies left hospitals in England wholly breast-fed and 95 per cent of the babies born in the districts were breast-fed when the midwife left the home. At the end of 3 months, however, 50 per cent of the babies, whether hospital or home-born, were breast-fed and at 6 months only 40 per cent were being nursed. McNeil (520) and Waller (936) found a similar situation in Scotland. Waller (936) cites figures from an infant welfare center in Bournmouth showing breast feeding in 53 per cent of 650 babies less than 3 months old. In a study of 1100 weanings in Liverpool,

Robinson (707) found that at least 53 per cent (583 infants) occurred within 1 month postpartum. It is noteworthy that in 40 per cent of the instances a cause could not be detected.

Stewart and Pratt (819) reported that 40 per cent of 900 women refused to nurse. Among the other mothers, the chances for full nursing were 65 to 74 per cent, depending upon the age of the mother, upon parity, and whether or not the baby was nursed from alternate or both breasts at each feeding. These authors report deficient lactation in about 14 per cent of the mothers attempting to nurse while in the hospital. No woman with deficient lactation was able to achieve complete breast nursing by the tenth postpartum day. Byington and Harmon (104, 105) concluded from hospital records that the incidence of breast feeding among women discharged from various Detroit area hospitals with newborn infants ranged from 5.6 to 69 per cent.

A study of 3721 infants in Stockholm by Rydberg (725) showed breast feeding entirely until the age of 6 months in 33 per cent and until the age of 9 months in 7 per cent. Sundal (835), in a study of the infants of 109 Oslo mothers, found breast feeding entirely until 6 months in 36 per cent and until 9 months in 29 per cent. In a series of 1962 Oslo mothers given postnatal care during the years 1940 to 1944 (903) the ability to breast feed completely reached 53 per cent at 6 months of age and 52 per cent at 9 months of age. The ability to lactate in a group of women given both prenatal and postnatal care ranged from 49 to 63 and 49 to 62 per cent at 6 and 9 months, respectively, during the same years. The prenatal care consisted of thorough health supervision with advice on meeting optimally the nutritional demands of pregnancy. All women were advised to supplement their diets with cod liver oil and brewer's yeast during pregnancy. Ebbs and co-workers (215) also recorded an improvement in lactation ability resulting from good prenatal diet: only 26 per cent of mothers whose prenatal diet was poor were able to breast feed their infants, in contrast to 47 per cent among mothers receiving good or supplemented diets during pregnancy.

As a result of the hunger period in Holland, Smith (791) found that the secretion of milk by mothers, considered solely as milk production sufficient to feed a baby, was not significantly influenced. In England, Waller (936) reported that following prenatal expression of colostrum during the last weeks of pregnancy 83 per cent of a group of mothers were able to nurse their babies for 6 months, compared with 43 per cent of another group of mothers.

Stewart and Pratt (818) suggested that the suckling stimulus may account for the higher incidence of full breast nursing among primiparas placing their babies early on both breasts, a suggestion supported by others (701, 757, 758). The complete emptying of the breasts also seems to exert a stimulating effect. Davies and Pratt (181) presented a simple technic for manual expression of human milk which will provide stimulation and maintenance of milk flow for many mothers. By means of manual expression and, in addition, drenching with hot and cold water and massage, King (428, 431) succeeded in reestablishing milk flow as a supplement to the baby's nursing 3 to 6 weeks after complete weaning.

Davies and Pratt (181) came to the conclusion that few excuses for not attempting to feed infants their mothers' milk are valid and stated that "with education of the mothers to their physical and nutritional needs, and with sufficient attention from

physicians and nurses, the number of babies that are breast-fed could be tremendously increased." Even in total absence of the suckling reflex some women with inverted nipples have successfully expressed their milk manually, milk flow persisting at a high level over 14 months (523). Macy and co-workers (523) also found a definite individual physiologic capacity of the mammary gland, both in the quantity of milk produced and in the length of time that lactation persisted under normal conditions. These authors stressed the necessity of an adequate prenatal diet, and found that protein retention during pregnancy greatly influenced the lactation ability of the mother.

Milk flow usually rises from about one-half liter daily after the first week or two of lactation to about one liter in the fifth month. The actual energy value of the milk formed would range from 330 to 660 calories per day according to Garry and Wood (279). Garry and Stiven (278) found that actual milk formation involved almost no expenditure of energy and for this reason allowed only 350 to 700 calories per day for lactation. Thus, 500 calories, the number recommended by the National Research Council for lactation, probably would be enough energy for the production of average yields of milk, provided that as lactation advances either efficiency increases or energy expenditure decreases. It is probably rather common that a nursing woman draws upon material normally stored during pregnancy. If the prenatal diet has been deficient the tissues may be drawn upon to such an extent that the flow of milk will be diminished or stopped.

The calcium intake recommended for lactating women by the Food and Nutrition Board, 2 gm. per day, can easily be obtained from a normal diet. Little emphasis is placed on phosphorus requirements because the 3 gm. of phosphorus per day which is desirable during lactation will be provided if the necessary calcium is supplied in natural foods.

The criterion to use in judging the requirement of a nutritional factor such as ascorbic acid during lactation is a problem. Saturation tests have shown (899) that during lactation a woman's requirement for this vitamin is maximal. Even with a high content of ascorbic acid in breast milk, the total daily secretion does not exceed 60 mg. Of the 150 mg. recommended daily during lactation, 90 mg. of ascorbic acid is required by the mother for her own metabolism. A daily intake of 150 mg. of ascorbic acid from natural foods may be provided easily in some countries, but in the northern European countries such an intake from natural foods is impossible in the winter and spring seasons when fresh fruit and vegetables are very scarce.

The League of Nations Technical Commission (1935) recommended an intake of 45 to 55 mg. of vitamin C per day during pregnancy and lactation. Subsequently (1936), they recommended that a diet adequate for pregnancy and lactation should contain at least 25 mg. ascorbic acid each day. In 1939, the Food and Drug Administration defined the minimum daily requirement for ascorbic acid, 80 mg., for both pregnancy and lactation. The Food and Nutrition Board of the National Research Council (1948) has recommended 100 mg. during pregnancy and 150 mg. during lactation. These figures illustrate the difference of opinion that exists as to the need of this factor during pregnancy.

Fehily (248, 249) and Stannus (813) have suggested that the milk from a woman

on a diet deficient in vitamin B is toxic to the baby as a result of the presence of methyl glyoxal. The sudden deaths of infants fed by mothers with deficient thiamine intakes are explained by this toxic substance. Even in countries where manifest beriberi is not seen, the possibility of secretion of this toxic substance in the milk must be recognized. Yamagishi and Sato (994) were first to suggest this explanation for the sudden deaths in breast-fed infants which do not occur in bottle-fed infants.

Tables of dietary allowances disregard carbohydrate and fat. According to Garry and Wood (279) it is desirable that the diet of a lactating woman contain at least 100 gm. of fat. It is generally agreed that the protein intake during lactation should be 2 gm. per kilogram of body weight per day. Despite such an ample allowance, breast feeding may lead to a negative nitrogen balance. Hunscher and co-workers (390) have, however, shown that under good nutritional conditions during pregnancy a woman stores a considerable amount of protein, which may avert negative balance during lactation (525). Whether negative nitrogen balance during early lactation is conditioned by an energy intake too low to meet demands is not known. Platt and Gin (668) observed that among the Chinese, an ample fluid intake with a diet rich in protein promoted lactation. On the other hand, Olsen (646) warns against a nursing woman taking more fluid than she desires.

Foster and co-workers (261) found that mice receiving a purified diet successfully reared 61 per cent of their young whereas stock animals reared 85 per cent. The addition of 2 per cent liver extract to the experimental diet was without effect. Ershoff (237) with rats receiving a purified diet observed normal growth and reproduction, but lactation failure. Rombouts and Querido (716) reported slightly subnormal growth in male rats ingesting a similar diet, and observed only 35 per cent success in lactation in females, although they considered reproduction satisfactory. In 1936, Cox and Imboden (152) concluded that satisfactory reproduction and lactation could be obtained with synthetic diets provided sufficient amounts of the vitamin B complex were added. For this they used an aqueous extract of brewer's yeast.

Zucker and Zucker (1004) observed normal growth in rats if they increased the crude protein content of the diet from 20 to 27 per cent. Troescher-Elam and Evans (908), on the other hand, noted no improvement in growth of mice when the level of extracted casein in a purified diet was increased. These findings indicate that impurities in commercial casein, not the protein contribution of the foodstuff, promoted the improved growth rate. In several experiments (119, 120, 925, 926) during lactation mother rats lost weight unless they received an addition of folic acid concentrates. Folley and co-workers (256) state that there was no improvement in lactation when pure biotin and folic acid were added to a highly purified diet consisting of extracted casein, sucrose, fat, salts, and solutions of vitamins A, D, E, and K and thiamine, riboflavin, pyridorine, calcium pantothenate, nicotinic acid, inositol, p-aminobenzoic acid, and choline. The addition of fresh liver, however, was followed by apparently normal growth, reproduction, and lactation. These authors conclude that for normal growth, reproduction, and lactation, the purified diet used, supplemented with the more readily available pure vitamins, requires further supplements, and that the factor (or factors) concerned is present in fresh liver, liver extracts, milk, and a biotin concentrate.

Mental strain and emotional factors seem to play some role in the ability of the mother to lactate. Although many investigators have considered this opinion rather than scientific truth, we know that milk flow may stop suddenly following a severe emotional stimulus producing anger, fear, or anxiety. The autonomic nervous system, possibly through the influence of the adrenals, may produce a constriction in the capillaries surrounding the secretory cells and thus render them less vital. When the emotional influence is repeated or persists this tension may continue and with the prolonged inhibition of the functional capacity of the cells diminished milk flow may proceed to complete cessation of mammary gland activity. Emotional response may explain some instances of sudden decrease in milk flow when the mother returns home from the hospital. In addition to resuming the responsibility of home management and the physical burden of housework after the period of rest in the hospital, the mother must assume the responsibility for the new baby and withstand any emotional stresses in the family and social relationships.

Lack of knowledge of the importance of breast feeding and false information also contribute to the decline in breast feeding. The fact that infant mortality is declining constantly in the United States may have produced erroneous impressions in the minds of many American physicians. It is true that breast milk is a product of the mother's diet and may, therefore, not be the ideal food in all circumstances. We know that premature infants thrive better on higher protein than breast milk contains. We also know that breast milk may contain inadequate amounts of various vitamins, making supplementation desirable. These facts do not nullify the fact that human milk is the food designed by Nature for the human infant, or circumvent the truth that our present knowledge has not enabled us to produce a formula for infant feeding which can be demonstrated to represent an improvement of Nature's product.

It is true that premature infants grow and develop better with higher protein intakes than breast milk provides—but prematurity is not a normal physiologic state. The premature infant is the fetus which is incompletely prepared for infancy and is in every respect less mature than is normal for the newborn infant. The nutritional stores and metabolic processes of the premature infant differ from those of the full-term infant: postnatal growth is more rapid and therefore nutritional requirements are relatively greater, while the ability to absorb and utilize the various food constituents is lower. The breast milk completely adequate in nourishing the full-term infant may not meet the nutritional requirements of the less-well-developed newborn infant. This does not detract from the many values of human milk but demonstrates the value of efforts to decrease the number of premature infants and to devise supplements which will make a "breast milk formula" as ideal for premature infants as the natural food is for fully developed newborn babies.

The collection and preservation of breast milk for infants to whom the opportunity of being fed by their mothers has been denied is particularly important for malnourished and sick infants. Evidence indicates that, in addition to the known components, there are in breast milk many yet unevaluated and undiscovered components which stimulate better absorption and utilization of food components, and the therapeutic value of human milk in some of the disturbances of early infancy is firmly established. The Committee on Mother's Milk of the American Academy of Pediatrics

has recommended standards for the operation of mothers' milk bureaus (139) which specify the organization of the bureaus, the personnel, the donors, the collection of mothers' milk, plant and equipment, handling of milk, and records and reports.

It is a question whether the contact with the infant which breast feeding provides is not equally as desirable, and even necessary, for the mother as for the infant. It gives a mother a feeling of satisfaction, security, and trust in herself which she needs in the future care of her child. Aldrich (13) says: "brea st-feeding is a physiologic maturation process for mothers. It is maintained that women benefit physiologically and psychologically by the accomplishment of this part of the normal development of maturity. In this intimate situation, as in no other, a mother obtains a demonstration of her real importance to the infant. She not only feels her importance but acts it. This is just as necessary to her mental health as it is to the baby's. . . . ."

The exigencies of modern living may require that a mother work outside the home; some mothers prefer to be independent and not be bound to a regular feeding schedule. Finally, some mothers may object to nursing their babies for emotional reasons or misconceptions about breast feeding. The time required for proper instruction of mothers and the ease of control offered by the technically well-developed artificial feeding procedures which apparently obtain good nutritional results in most instances have made many physicians and nurses feel justified in advocating formula feeding in preference to breast feeding. In hospitals many infants are not even put to the breast because the doctors and nurses do not encourage breast feeding. The mothers, trusting those medically trained, do not insist and both mother and infant are deprived of the physical and emotional values without trial.

In these days when proprietary infant foods try to make up for Nature's food we might remember Oliver Wendell Holmes' statement: "A pair of substantial mammary glands have the advantage over the two hemispheres of the most learned professor's brain in the art of compounding a nutritive fluid for infants." In an editorial (219) in the *Journal of the American Medical Association*, where the foregoing statement was cited, the author adds: "Perhaps in these days when hypofunction of the postpartum breast is a national phenomenon, refuge in the cerebral hemispheres of the learned physician is necessary." The editorial reminds, though, that the physician must know the nutritional value of the food given, otherwise deficiency diseases such as rickets and scurvy may result.

FUTURE PROGRAM

As conditions are throughout the world today, the reproductive period is not a safe one for the prospective mother nor for her infant. Many pregnancies result in death for one or the other, or both,—or in defective offspring. With our present knowledge, the majority of these deaths and physical or mental cripplings are preventable. Prevention requires that the physiology of reproduction must be generally known and that the knowledge must be applied.

Further research work in the physiology of reproduction must be stimulated. Such research work may consist of further development of mass studies already in progress or initiation of long-time studies of individual nutritional factors. In efforts to understand the etiology of conditions in mothers and fetuses, cooperation among

the various groups in medicine and the allied sciences is of major importance. The same mothers and their infants must be studied from various clinical points of view, accompanied by thorough, extensive nutritional investigations. The nutritional, environmental, and mental backgrounds of mothers must be explored. Future research work must clarify the etiology of the three main causes of stillbirths, neonatal deaths, and physically and mentally defective children: (1) prematurity, (2) malformations, (3) birth injuries. Mothers must be studied throughout the prematernal and the prenatal periods and infants must be followed throughout the years of life.

The figures from ruling families in previous years demonstrated plainly that in infant mortality, both neonatal and total, we are dealing with factors as much social and economic in character as they are medical. It should be possible to lower infant mortality in a whole population by improving environmental conditions within families and adjusting them to benefit mothers and infants. Infant mortality was decreasing consistently by improvement in the social conditions of some countries prior to the war. As we know, the war caused an abrupt change in the trend of mortality figures for central and southern Europe. In Great Britain, however, conditions improved as a result of food rationing which provided better nourishment of mothers and children of the lower income classes.

Stillbirths are an important part of the "reproductive wastage" which Yerushalmy (998) deplored. Pregnancy either very early or very late in a woman's reproductive life predisposes to stillbirths, since age of the mother is a factor even more important than order of birth. Until more uniform collection of stillbirth information is achieved, the total picture of infant losses will be incomplete, but there still remains a great deal to be done in lowering the occurrence of stillbirths by prevention of complications in pregnancy and emphasis upon correct nutrition and suitable prenatal conditions for the mother.

Prematurity heretofore has been considered from the therapeutic rather than the preventive or prophylactic point of view. In modern pediatric departments separate facilities are installed to give the very best care to these immature infants who are ill-prepared for independent life and are very susceptible to various morbid conditions. All "follow-up" studies agree that a large percentage of such infants also are mentally backward, although some of our most talented and brilliant minds have belonged to people who started life as premature infants. Still, more and more premature infants will survive because medical care is constantly improving. An increasing number of very small prematures are saved, but these are the infants who later show greatest lack in development.

Investigations have confirmed that prematurity is attributable to a combination of various factors, including those of nutritional, mental, or social character, which influence the general well-being of the mother. By studying the growth of the fetus and investigating the full nutritive requirement of the mother and fetus, the problem of prematurity will be solved and fetal and neonatal infant mortality and morbidity will be lowered. The constant improvement in the care of these infants is a contribution to pediatric knowledge, but it is the prevention of their premature delivery which must be the ultimate objective. If a positive result is to be gained in reduction of premature births, attention must be paid to the environmental stresses, as well as

to the nutritional status of pregnant women. Social and financial security are of the greatest importance in this connection. The better the care of pregnant women, the lower the stillbirth and neonatal mortality rates, and the better the general health of newborn infants.

The losses to society of potential infants through abortions is entirely unknown. Research on causes for spontaneous and habitual abortion is being carried out; indication for therapeutic abortion occurs at the present time because of such complications in pregnancy as tuberculosis, toxemia, and heart disease. The work of Swan and associates (840, 842, 843, 844, 845) and Gregg (315, 316) on the etiology of congenital anomalies emphasized the influence of virus diseases, particularly rubella, upon the development of the fetus. Cases of congenital defects have also been noted as results of measles (264), poliomyelitis (29), and infectious mononucleosis (462) during pregnancy. Greenhill (312), in discussing methods to reduce the incidence of monstrous births, suggested that: women who have had one monster should not have other children since their chances of repetition are 24 times the average ratio of 47 per 10,000 in the general population; the childbearing age should be kept under between 30 to 35 years, as the outside limit, since the incidence of gross abnormalities rises above 35; and consideration should be given therapeutic abortion for rubella contracted during the first trimester of pregnancy.

The conflict which some investigators see between theories of genetic and nutritional origin of malformations may not exist. Dann (167, 168, 169, 170, 171) pointed out almost 20 years ago that developmental processes can be altered by environmental disturbances, with a resulting reduction in growth similar to that produced by abnormal genes. Genes, or parts or areas of genes, Warkany suggests may act as enzymes or catalysts, absorbing specific protoplasmic substances. Knowing that vitamins act as components of enzymes in the body we may visualize a vitamin deficiency and a defective gene having identical effects and leading to the same congenital abnormality.

All these facts must be considered in relation to the nutritional state of the pregnant woman. The importance of the prematernal store influenced by family eating patterns may be evaluated not only from a genetic but also from a nutritional point of view. A girl who has not completed her growth, and whose nutrition may not be adequate for her own body, could not be expected to develop a good fetus. An older woman may have depleted her store of food factors. Similarly, a woman whose dietary pattern is habitually poor would become more depleted with each succeeding pregnancy and lactation period. Thus, familial tendencies in pathological conditions are not necessarily genetic, but may result from poor food habits of long duration.

For a new life to be started well it is evident that the maternal body must be rebuilt after each pregnancy and lactation period, making of primary importance, for the mother, the fetus, and the newborn infant, a proper rest period between reproductive cycles. The desirable length of the reparative period is dependent upon general health, nutritional status, and emotional influences in the envoronment. The contraceptive techniques in general use in all civilized countries constitute a means by which intervals between pregnancies may be regulated. We know these measures are not 100 per cent effective and some are not wholly innocuous, but competent instruction can be given and suitable contraceptives can be prescribed by physicians

familiar with the adverse effects of many preparations in common use. More research should be encouraged to clarify the possible uses, abuses, and dangers of various contraceptives used to avoid pregnancy when contraindicated by the condition of the mother.

Animal studies show that in early pregnancy nutritional deficiencies of the mother result in defective offspring. The conditions found in human mothers who bear malformed infants are so similar to those found in animals with deficiencies early in gestation that the same origins seem highly probable. At the stage of gestation in which these conditions occur, the mothers often do not know they are pregnant and have not yet sought medical advice. For this reason, prenatal supervision should start very early in, preferably before, pregnancy. Prenatal care involves prematernal care, supervision of the years preceding pregnancy, for those years determine the general health and the store of nutritional factors in the mother organism. Prenatal care, then, is a very important part of the effort to make the female body a fit environment for complete and harmonious growth of the fetus at a time when the total metabolic economy of the pregnant woman is disrupted. The disturbances (morning sickness, etc.) commence with the imbedding of the zygote in the uterine mucosa about the eighth to tenth day after fertilization, coincident with the establishment of a new endocrine pattern in the mother.

It is important to realize that the mother and fetus form a unity and in research they must be considered together. An effect upon one may affect the other but how severe a maternal deficiency must be before the fetus is affected is unknown. The fetus may be affected more severely than the mother. A mother with latent beriberi may give birth to a child with congenital beriberi. Iodine deficiency which causes only enlargement of the thyroid gland in the mother may produce cretinism in the child. Many factors are involved in deficiencies during pregnancy: nausea, vomiting, perverted appetite, drugs and medicines, infections, and mental strain.

The whole mother-child unit may be affected in various ways, for example, the structure or function of one organ may be altered without any others being influenced. The theory about the parasitic condition of the fetus certainly is not true. From study of various malformations we know that localized deficiencies may produce irreparable results in the rapidly growing ovum without observable symptoms in the mature maternal organism. These minimal deficiencies in the mother, however, may later be demonstrated by a definite and manifest symptom complex which is the end result of long-lasting deficiency. Quite possibly acute undernutrition may have one result and chronic malnutrition produce another. Unbalanced diets seem more distinctive than plain starvation. The need for careful consideration of the time factor in nutritional studies of pregnancy is strongly suggested. It is also obvious that fetal growth may be related to the maternal caloric intake of later pregnancy, whereas fetal development and viability may rest, nutritionally speaking, as much upon the maternal circumstances before conception as upon those of pregnancy itself. This fact is of particular interest because both in experimental and in clinical studies the data accumulated show the importance of the prematernal period to the development, the viability, and the future progress of the new generation.

It has become more and more clear that the term "birth asphyxia" is loosely used

in medical practice regardless of the etiological factors involved (744). Over 20 years ago Cruickshank (156) considered asphyxia with birth injuries, and recent experimental work (394) has clarified the role of anoxia as a teratogenic agent. A thorough prenatal history evaluating general health, nutritional and emotional factors, and proper consideration of all factors during labor, will clarify the causes of many of the mental and motor disturbances seen in children at present.

Experimental as well as clinical studies are needed to clarify the rather obscure but very important hemorrhagic tendency in fetal life and in newborn infants. The delivery process should be studied and recorded as accurately as possible. The prothrombin content of the blood of the infant during the first week after birth must be studied intensively, supplemented with a thorough nutritional and clinical history of the mother for the present pregnancy and for the whole prematernal period. The eyegrounds of all infants should be observed for at least the first 2 years of life in order to detect any symptoms of central nervous system disturbance. Those showing neurological disturbances must be studied thoroughly by encephalographic and perhaps by angiographic methods to determine possible damage to the brain. Living infants and their mothers should be studied; in addition, infants stillborn and those dying in the neonatal period should be sectioned and studies made of the brain, spinal cord, and other parts of the body showing possible hemorrhages. If such observations could be made over a period of years we would have a basis for evaluating procedures for the prevention of central nervous system damage in early or later infancy and childhood.

Whether its connection with the blood prothrombin content, and thereby blood coagulation, is the only function of vitamin K in the body, and whether the animal experiments showing vascular changes from vitamin K deficiency have significance in human physiology and pathology are important questions. High stillbirth rate, neonatal death rate, and cerebral damage as a result of changes in the cells of the brain and vessel walls resulting in various forms of spastic palsies may be linked with vitamin K. This fat-soluble vitamin also may require consideration in relation to other nutritional factors which influence the cells in the brain and vascular bed, such as vitamin E and thiamine.

The Rh factor at times threatens the life of the fetus and of the newborn infant. According to Levine and co-workers (469, 470), in the typical case the father is Rh positive, the mother is Rh negative, and the fetus is Rh positive, the Rh factor having been inherited from the father. The incompatible fetal blood entering the circulation of the mother results in formation of agglutinins which return to the fetus and combine with the fetal Rh-positive red blood cells, giving rise to various forms of hemolytic disease. The incidence of this disease, according to Wiener (974) is about one in 300 deliveries. Sensitization to the Rh factor does not affect the first pregnancy unless there has been a previous transfusion of the mother. But once sensitization develops it seems to be permanent, though there is difference in the degree of sensitization. These hemolytic diseases occur, therefore, usually in later pregnancies. Some Rh-negative mothers have repeated stillbirths while others have viable infants who recover after transfusion therapy. Preventive work should include systematic examination of all pregnant women for determination of Rh factors.

We do not yet have sufficient channels through which to penetrate the population. The medical profession and the community have been busy for so many years helping the sick and damaged mothers and children that exploration of the possibilities of preventing manifest diseases has been limited to small groups of scientists. To spread this knowledge in the interest of future health requires strong, positive attitudes by public health departments in states and cities, for from these departments the work must be directed. Skilled, trained personnel with a positive attitude towards preventive medicine are essential.

The general practitioner, the obstetrician, and the pediatrician are closest to mothers and children. Education in medical schools at present does not emphasize phophylaxis sufficiently. Few schools have teachers of preventive medicine and prophylactic pediatrics. Boudreau and Kruse (71) stated that the real restriction to progress in the nutrition programs of state health departments is the unavailability of qualified physicians. The general laws of reproduction, growth, and development should be included in the teaching program of all medical students early in their training. Medical students should be taught all the known factors involved in the development of a normal person and all the factors known to minimize the chances of departure from normal. As an auxiliary to the obstetric and pediatric departments, both of which now teach normal growth and development, as well as healing the various deviations from normal, a prophylactic division is a logical expansion, established to teach students the laws of growth and development and the manner in which these are affected by prematernal and maternal nutrition, health, and environment.

The great question is how prenatal care should be organized to meet the need of women most in need of direction and help. This kind of supervision must be established in such a way that the whole population understands that it is desirable and necessary. A compulsory arrangement may create opposition. Thorough and intelligent education in all communities, through schools, through classes for mothers, and classes for adolescents, in close cooperation with local physicians and health authorities, will create a positive attitude in the population.

Erection of health centers for mothers and children has proved of great benefit in some countries. In countries where the hospital system is well-developed, such centers may be a part of the university hospitals which naturally will be training centers for medical, dental, and nutrition students and for nurses. In countries where hospitals are scarce and less well-equipped, the public health service may establish such prophylactic institutions for mother and child as separate entities in the community. We know that infancy forms only a very minor part of the whole growth period. To make prophylaxis efficient, supervision must be made continuous from conception to the end of growth in length and reproduction requirement. Such institutions may share in educating the medical student and also educate the whole population in the laws of growth and development.

In Norway prenatal care has been the responsibility of infant welfare centers, with a plan that the centers should be expanded to cover the whole growth period of the child. Since this supervision and the knowledge of its value were considered a part of everybody's education, it was found natural to plan these health centers as separate parts of the public schools as new schools are erected. In the suburbs now

a part of Oslo, prenatal care will form a division of the health centers in the public schools, supervising the entire growth period from conception through the twentieth year. Children in the adolescent period may come under regular supervision, thus preparing the female body before and up to the childbearing age. When the prenatal period is supervised, combined with supervision of the child's growth, a more uniform prospect is gained for the development of every individual.

Each health department should have separate units for mother and child, led by a medical director well-trained in all aspects of reproduction, growth, and development. Such a department would have authority and be respected by the population. Of the six basic functions for a local health department, Emerson and Luginbuhl (233) place fifth the hygiene of maternity, infancy, and childhood. Dental students also must be acquainted with normal development and mineralization of teeth and how to prevent tooth destruction, and prophylactic dental work also must be supported so that a dentist can be a part of each public health department. The nutritionist who has received all of his training in nutrition is a valuable member of a health program. Nutritionists comprise a group characteristic of American science and have proved their great value in all public health work. From health departments efforts should be made to reach all health units, private or official, all teaching institutions or associations through which the gospel may be spread so the facts may be known. Wilkins (976) has recently expressed it thus: "Separate the true from the false and set out to demonstrate the facts through all available channels."

It is a question whether the time has not come when prophylactic medicine, which has such far-reaching possibilities in the development of each individual, for the general medical knowledge, and for the well-being of the population, should not be given a broad place in medical schools. It is the medical student who must be acquainted with this branch of medical knowledge and the prospects of its application. Prophylactic Pediatrics is the fundamental pillar in the future of Medicine. Only in the prematernal period is a good foundation laid for prevention of deficiencies and their consequences, morbidity and mortality for mother and child.

There may be some objection to inclusion of pediatrics in a concept of prophylactic maternal care, for the prenatal period usually is considered the obstetrician's field. Pregnancy, however, is a very complex situation which needs supervision by a physician with obstetrical skill and a thorough knowledge of the nutritional requirements of the maternal and fetal organisms. A physician trained in prophylactic pediatrics, familiar with prematernal nutritional requirements and development, will, in close cooperation with the obstetrician, be able to serve the double organism as growth proceeds. In the health center for mother and child in Oslo such cooperation has proved very practical, the obstetrician and the pediatrician each taking his natural role in the examinations of the mother and being acquainted with the physiologic processes occurring in the prenatal period, factors which have great bearing on the postnatal development of the infant. Otherwise, a pediatrician often lacks the deeper insight into the full development of the child which would help him in early diagnosis and, therefore, with early treatment of deviations from normal.

It cannot be denied that one of the most disappointing and disquieting features in health work for mothers and infants is the steady decline in the number of nursing

mothers. The physician caring for the mothers during pregnancy may, through preparatory procedures (conferences, demonstrations, and provision of reading material), create positive attitudes towards nursing in mothers before delivery. Complete hygiene during pregnancy consists also in preparing for the proper feeding of the newborn infant. When it is separated from its internal nourishment through the placenta, the mother's body should be ready to provide the external nourishment through the mammary glands.

Good parent education and sound knowledge of the physiological processes going on in her body are preventive measures to combat any woman's emotional and nervous influences. The nutritional needs of the child, the choice of proper foods to meet these needs, together with knowledge of amounts necessary at each age level, may form an important part of a program for the education of parents. In teaching, it is well to consider the fathers as well as the mothers because the food prejudices and attitudes of both parents influence those of their children.

Jolliffe (411) pointed out that nutrition can reach the school child by providing him with a school lunch containing one-third to one-half of the daily dietary requirements. Such lunches compensate for home dietary deficiencies and cultivate proper food likes and dietary habits. In Scandinavian countries school lunches ("Oslo breakfast") have been furnished for many years with very satisfactory results. In addition to the direct nutritional value of the school lunch for the individual child, an effective influence toward improved nutrition in his family group is achieved. Jolliffe also emphasized that school health facilities should be expanded so that nutritional inadequacies can be detected and corrected before they impair the health of the child. Finally, he suggested erection in the health departments of nutrition clinics which should have preventive, diagnostic, and therapeutic aims. Such a clinic was started in March 1945 in the Department of Health of the City of New York.

There is no reason why this knowledge should not be a part of the theoretical knowledge given the child in school. In a small country such as Norway, where the hospitals are scattered and often not as well-equipped as in other countries, a law in one of the largest southern communities of the country requires that in newly erected schools such health centers for mothers and children be established. Thus, supervision is planned for the whole growth period of a human being, from conception to end of the growth period. The theoretical and practical knowledge of how to build a sound body and mind will thus be part of the whole school system. Teachers, doctors, and health authorities are working together under the supervision of the health department in erecting a good understanding of what physical and mental health is and how to gain it. With separate entrance for mothers, small children, and adolescents in wings of the school building, this supervision will not interfere with the regular teaching program in other parts of the building. In this way the supervision for the whole period of growth will come under one administration. The results gained at such centers may be uniformly evaluated, and material of great importance for further knowledge in the developmental processes throughout the whole growth period may be gained. Such material will form the basis for future work with maternal and child health.

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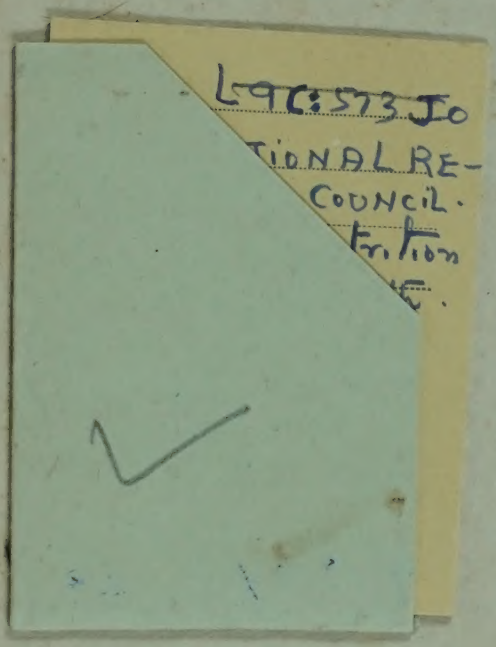
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